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(54) Title: <b>INHIBITORS OF INTERLEUKIN-1<math>\beta</math> CONVERTING ENZYME</b>			
(57) Abstract			
<p>The present invention relates to novel classes of compounds which are inhibitors of interleukin-1<math>\beta</math> converting enzyme. The ICE inhibitors of this invention are characterized by specific structural and physicochemical features. This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting ICE activity and consequently, may be advantageously used as agents against IL-1-, apoptosis-, IGIF-, and IFN-<math>\gamma</math>- mediated diseases, inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases, degenerative diseases, and necrotic diseases. This invention also relates to methods for inhibiting ICE activity, for treating interleukin-1-, apoptosis-, IGIF- and IFN-<math>\gamma</math>-mediated diseases and decreasing IGIF and IFN-<math>\gamma</math> production using the compounds and compositions of this invention. This invention also relates to methods for preparing N-acylamino compounds.</p>			

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INHIBITORS OF INTERLEUKIN-1 $\beta$  CONVERTING ENZYMETECHNICAL FIELD OF THE INVENTION

The present invention relates to novel  
5 classes of compounds which are inhibitors of  
interleukin-1 $\beta$  converting enzyme ("ICE"). This  
invention also relates to pharmaceutical compositions  
comprising these compounds. The compounds and  
pharmaceutical compositions of this invention are  
10 particularly well suited for inhibiting ICE activity  
and consequently, may be advantageously used as agents  
against interleukin-1- ("IL-1"), apoptosis-, interferon  
gamma inducing factor- ("IGIF") and interferon- $\gamma$ -  
("IFN- $\gamma$ ") mediated diseases, including inflammatory  
15 diseases, autoimmune diseases, destructive bone,  
proliferative disorders, infectious diseases and  
degenerative diseases. This invention also relates to  
methods for inhibiting ICE activity, and decreasing  
IGIF production and IFN- $\gamma$  production and methods for  
20 treating interleukin-1-, apoptosis-, IGIF- and IFN- $\gamma$ -  
mediated diseases using the compounds and compositions  
of this invention. This invention also relates to  
methods of preparing N-acylamino compounds.

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BACKGROUND OF THE INVENTION

Interleukin 1 ("IL-1") is a major pro-inflammatory and immunoregulatory protein that stimulates fibroblast differentiation and proliferation, the production of prostaglandins, collagenase and phospholipase by synovial cells and chondrocytes, basophil and eosinophil degranulation and neutrophil activation. Oppenheim, J.H. et al, Immunology Today, 7, pp. 45-56 (1986). As such, it is involved in the pathogenesis of chronic and acute inflammatory and autoimmune diseases. For example, in rheumatoid arthritis, IL-1 is both a mediator of inflammatory symptoms and of the destruction of the cartilage proteoglycan in afflicted joints. Wood, D.D. et al., Arthritis Rheum. 26, 975, (1983); Pettipher, E.J. et al., Proc. Natl. Acad. Sci. UNITED STATES OF AMERICA 71, 295 (1986); Arend, W.P. and Dayer, J.M., Arthritis Rheum. 38, 151 (1995). IL-1 is also a highly potent bone resorption agent. Jandiski, J.J., J. Oral Path 17, 145 (1988); Dewhirst, F.E. et al., J. Immunol. 8, 2562 (1985). It is alternately referred to as "osteoclast activating factor" in destructive bone diseases such as osteoarthritis and multiple myeloma. Bataille, R. et al., Int. J. Clin. Lab. Res. 21(4), 283 (1992). In certain proliferative disorders, such as acute myelogenous leukemia and multiple myeloma, IL-1 can promote tumor cell growth and adhesion. Bani, M.R., J. Natl. Cancer Inst. 83, 123 (1991); Vidal-Vanaclocha, F., Cancer Res. 54, 2667 (1994). In these disorders, IL-1 also stimulates production of other cytokines such as IL-6, which can modulate tumor development (Tartour et al., Cancer Res. 54, 6243 (1994). IL-1 is predominantly produced by peripheral blood monocytes as part of the inflammatory response



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and exists in two distinct agonist forms, IL-1 $\alpha$  and IL-1 $\beta$ . Mosely, B.S. et al., Proc. Nat. Acad. Sci., 84, pp. 4572-4576 (1987); Lonnemann, G. et al., Eur. J. Immunol., 19, pp. 1531-1536 (1989).

5 IL-1 $\beta$  is synthesized as a biologically inactive precursor, pIL-1 $\beta$ . pIL-1 $\beta$  lacks a conventional leader sequence and is not processed by a signal peptidase. March, C.J., Nature, 315, pp. 641-647 (1985). Instead, pIL-1 $\beta$  is cleaved by  
10 interleukin-1 $\beta$  converting enzyme ("ICE") between Asp-116 and Ala-117 to produce the biologically active C-terminal fragment found in human serum and synovial fluid. Sleath, P.R., et al., J. Biol. Chem., 265, pp. 14526-14528 (1992); A.D. Howard et al., J.  
15 Immunol., 147, pp. 2964-2969 (1991). ICE is a cysteine protease localized primarily in monocytes. It converts precursor IL-1 $\beta$  to the mature form. Black, R.A. et al., FEBS Lett., 247, pp. 386-390 (1989); Kostura, M.J. et al., Proc. Natl. Acad. Sci. UNITED STATES OF  
20 AMERICA, 86, pp. 5227-5231 (1989). Processing by ICE is also necessary for the transport of mature IL-1 $\beta$  through the cell membrane.

ICE, or its homologs, also appears to be involved in the regulation of programmed cell death or  
25 apoptosis. Yuan, J. et al., Cell, 75, pp. 641-652 (1993); Miura, M. et al., Cell, 75, pp. 653-660 (1993); Nett-Fiordalisi, M.A. et al., J. Cell Biochem., 17B, p. 117 (1993). In particular, ICE or ICE homologs are thought to be associated with the regulation of  
30 apoptosis in neurodegenerative diseases, such as Alzheimer's and Parkinson's disease. Marx, J. and M. Baringa, Science, 259, pp. 760-762 (1993); Gagliardini, V. et al., Science, 263, pp. 826-828 (1994).  
Therapeutic applications for inhibition of apoptosis

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may include treatment of Alzheimer's disease, Parkinson's disease, stroke, myocardial infarction, spinal atrophy, and aging.

ICE has been demonstrated to mediate apoptosis (programmed cell death) in certain tissue types. Steller, H., Science, 267, p. 1445 (1995); Whyte, M. and Evan, G., Nature, 376, p. 17 (1995); Martin, S.J. and Green, D.R., Cell, 82, p. 349 (1995); Alnemri, E.S., et al., J. Biol. Chem., 270, p. 4312 (1995); Yuan, J. Curr. Opin. Cell Biol., 7, p. 211 (1995). A transgenic mouse with a disruption of the ICE gene is deficient in Fas-mediated apoptosis (Kuida, K. et al., Science 267, 2000 (1995)). This activity of ICE is distinct from its role as the processing enzyme for pro-IL1 $\beta$ . It is conceivable that in certain tissue types, inhibition of ICE may not affect secretion of mature IL-1 $\beta$ , but may inhibit apoptosis.

Enzymatically active ICE has been previously described as a heterodimer composed of two subunits, p20 and p10 (20kDa and 10kDa molecular weight, respectively). These subunits are derived from a 45kDa proenzyme (p45) by way of a p30 form, through an activation mechanism that is autocatalytic. Thornberry, N.A. et al., Nature, 356, pp. 768-774 (1992). The ICE proenzyme has been divided into several functional domains: a prodomain (p14), a p22/20 subunit, a polypeptide linker and a p10 subunit. Thornberry et al., supra; Casano et al., Genomics, 20, pp. 474-481 (1994).

Full length p45 has been characterized by its cDNA and amino acid sequences. PCT patent applications WO 91/15577 and WO 94/00154. The p20 and p10 cDNA and amino acid sequences are also known. Thornberry et al., supra. Murine and rat ICE have also been sequenced and cloned. They have high amino acid and

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nucleic acid sequence homology to human ICE. Miller, D.K. et al., Ann. N.Y. Acad. Sci., 696, pp. 133-148 (1993); Molineaux, S.M. et al., Proc. Nat. Acad. Sci., 90, pp. 1809-1813 (1993). The three-dimensional  
5 structure of ICE has been determined at atomic resolution by X-ray crystallography. Wilson, K.P., et al., Nature, 370, pp. 270-275 (1994). The active enzyme exists as a tetramer of two p20 and two p10 subunits.

10 Additionally, there exist human homologs of ICE with sequence similarities in the active site regions of the enzymes. Such homologs include TX (or ICE<sub>rel-II</sub> or ICH-2) (Faucheu, et al., EMBO J., 14, p. 1914 (1995); Kamens J., et al., J. Biol. Chem., 270, p. 15250 (1995); Nicholson et al., J. Biol. Chem., 270  
15 15870 (1995)), TY (or ICE<sub>rel-III</sub>) (Nicholson et al., J. Biol. Chem., 270, p. 15870 (1995); ICH-1 (or Nedd-2) (Wang, L. et al., Cell, 78, p. 739 (1994)), MCH-2, (Fernandes-Alnemri, T. et al., Cancer Res., 55, p. 2737  
20 (1995), CPP32 (or YAMA or apopain) (Fernandes-Alnemri, T. et al., J. Biol. Chem., 269, p. 30761 (1994); Nicholson, D.W. et al., Nature, 376, p. 37 (1995)), and CMH-1 (or MCH-3) (Lippke, et al., J. Biol. Chem., (1996); Fernandes-Alnemri, T. et al., Cancer Res.,  
25 (1995)). Each of these ICE homologs, as well as ICE itself, is capable of inducing apoptosis when overexpressed in transfected cell lines. Inhibition of one or more of these homologs with the peptidyl ICE inhibitor Tyr-Val-Ala-Asp-chloromethylketone results in  
30 inhibition of apoptosis in primary cells or cell lines. Lazebnik et al., Nature, 371, p. 346 (1994). The compounds described herein are also capable of inhibiting one or more homologs of ICE (see Example 5). Therefore, these compounds may be used to inhibit  
35 apoptosis in tissue types that contain ICE homologs, but which do not contain active ICE or produce mature

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IL-1 $\beta$ .

Interferon-gamma inducing factor (IGIF) is an approximately 18-kDa polypeptide that stimulates T-cell production of interferon-gamma (IFN- $\gamma$ ). IGIF is  
5 produced by activated Kupffer cells and macrophages in vivo and is exported out of such cells upon endotoxin stimulation. Thus, a compound that decreases IGIF production would be useful as an inhibitor of such T-cell stimulation which in turn would reduce the levels  
10 of IFN- $\gamma$  production by those cells.

IFN- $\gamma$  is a cytokine with immunomodulatory effects on a variety of immune cells. In particular, IFN- $\gamma$  is involved in macrophage activation and Th1 cell selection (F. Belardelli, APMIS, 103, p. 161 (1995)).  
15 IFN- $\gamma$  exerts its effects in part by modulating the expression of genes through the STAT and IRF pathways (C. Schindler and J.E. Darnell, Ann. Rev. Biochem., 64, p. 621 (1995); T. Taniguchi, J. Cancer Res. Clin. Oncol., 121, p. 516 (1995)).

Mice lacking IFN- $\gamma$  or its receptor have multiple defects in immune cell function and are resistant to endotoxic shock (S. Huang et al., Science, 259, p. 1742 (1993); D. Dalton et al., Science, 259, p. 1739 (1993); B. D. Car et al., J. Exp. Med., 179, p. 1437 (1994)). Along with IL-12, IGIF appears to be  
25 a potent inducer of IFN- $\gamma$  production by T cells (H. Okamura et al., Infection and Immunity, 63, p. 3966 (1995); H. Okamura et al., Nature, 378, p. 88 (1995); S. Ushio et al., J. Immunol., 156, p. 4274 (1996)).

30 IFN- $\gamma$  has been shown to contribute to the pathology associated with a variety of inflammatory, infectious and autoimmune disorders and diseases. Thus, compounds capable of decreasing IFN- $\gamma$  production

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would be useful to ameliorate the effects of IFN- $\gamma$  related pathologies.

The biological regulation of IGIF and thus IFN- $\gamma$  has not been elucidated. It is known that IGIF is synthesized as a precursor protein, called "pro-IGIF". It has been unclear, however, how pro-IGIF is cleaved and whether its processing has biological importance.

Accordingly, compositions and methods capable of regulating the conversion of pro-IGIF to IGIF would be useful for decreasing IGIF and IFN- $\gamma$  production in vivo, and thus for ameliorating the detrimental effects of these proteins which contribute to human disorders and diseases.

However, ICE and other members of the ICE/CED-3 family have not previously been linked to the conversion of pro-IGIF to IGIF or to IFN- $\gamma$  production in vivo.

ICE inhibitors represent a class of compounds useful for the control of inflammation or apoptosis or both. Peptide and peptidyl inhibitors of ICE have been described. PCT patent applications WO 91/15577; WO 93/05071; WO 93/09135; WO 93/14777 and WO 93/16710; and European patent application 0 547 699. Such peptidyl inhibitors of ICE has been observed to block the production of mature IL-1 $\beta$  in a mouse model of inflammation (vide infra) and to suppress growth of leukemia cells *in vitro* (Estrov et al., Blood 84, 380a (1994)). However, due to their peptidic nature, such inhibitors are typically characterized by undesirable pharmacologic properties, such as poor cellular penetration and cellular activity, poor oral absorption, poor stability and rapid metabolism. Plattner, J.J. and D.W. Norbeck, in Drug Discovery

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Technologies, C.R. Clark and W.H. Moos, Eds. (Ellis Horwood, Chichester, England, 1990), pp. 92-126. This has hampered their development into effective drugs.

Non-peptidyl compounds have also been  
5 reported to inhibit ICE in vitro. PCT patent application WO 95/26958; US Patents 5,552,400; Dolle et al., J. Med. Chem., 39, pp. 2438-2440 (1996); However, it is not clear whether these compounds have the appropriate pharmacological profile to be  
10 therapeutically useful.

Additionally, current methods for the preparation of such compounds are not advantageous. These methods use tributyltin hydride, a toxic, moisture sensitive reagent. Thus, these methods are  
15 inconvenient to carry out, pose a health risk and create toxic-waste disposal problems. Furthermore, it is difficult to purify compounds prepared by these methods.

Accordingly, the need exists for compounds  
20 that can effectively inhibit the action of ICE *in vivo*, for use as agents for preventing and treating chronic and acute forms of IL-1-mediated diseases, apoptosis-, IGIF-, or IFN- $\gamma$ -mediated diseases, as well as inflammatory, autoimmune, destructive bone,  
25 proliferative, infectious, or degenerative diseases. The need also exists for methods of preparing such compounds.

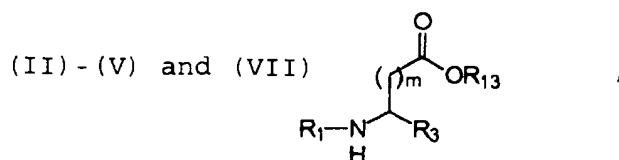
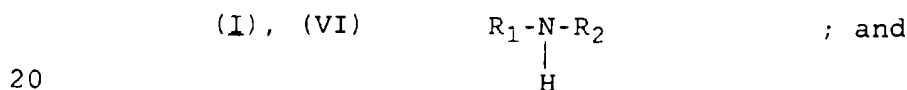
#### SUMMARY OF THE INVENTION

The present invention provides novel classes  
30 of compounds, and pharmaceutically acceptable derivatives thereof, that are useful as inhibitors of ICE. These compounds can be used alone or in combination with other therapeutic or prophylactic agents, such as antibiotics, immunomodulators or other  
35 anti-inflammatory agents, for the treatment or

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prophylaxis of diseases mediated by IL-1, apoptosis, IGIF or IFN- $\gamma$ . According to a preferred embodiment, the compounds of this invention are capable of binding to the active site of ICE and inhibiting the activity of that enzyme. Additionally, they have improved cellular potency, improved pharmacokinetics, and/or improved oral bioavailability compared to peptidyl ICE inhibitors.

It is a principal object of this invention to provide novel classes of compounds which are inhibitors of ICE represented by formulas:



wherein the various substituents are described herein.

It is a further object of this invention to provide a process of preparing N-acylamino compounds by coupling a carboxylic acid with an alloc-protected amine.

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BRIEF DESCRIPTION OF THE DRAWINGS

**Fig. 1A** ICE cleaves pro-IGIF in vivo. Cell lysates from Cos cells transfected with the various indicated expression plasmids or controls were analyzed for the presence of IGIF by separating proteins by SDS-PAGE and immunoblotting with anti-IGIF antisera (lane 1, mock transfected cells; lane 2, pro-IGIF alone; lanes 3-12, pro-IGIF in combination with ICE, ICE-C285S, CPP32, CPP32-C163S, CMH-1, CMH-1-C186S, Tx, Tx-C258S, respectively). Mobilities of pro-IGIF and the 18-kDa mature IGIF are indicated on the right. Molecular weight markers in kDa are shown on the left (Example 23).

**Fig. 1B** ICE cleaves pro-IGIF at the authentic processing site in vitro as shown by Coomassie blue staining of proteolytic reaction products separated by SDS-PAGE (Example 23). The proteases and inhibitors used were: lane 1, buffer control; lane 2, 0.1 nM ICE; lane 3, 1 nM ICE; lanes 4 and 5, 1 nM ICE with 10 nM Cbz-Val-Ala-Asp-[(2,6-dichlorobenzoyl)oxy]methyl ketone and 100 nM Ac-Tyr-Val-Ala-Asp-aldehyde, respectively; lanes 6 and 7, 15 nM CPP32 with and without 400 nM Ac-Asp-Glu-Val-Asp-aldehyde (D. W. Nicholson et al., Nature, 376, p. 37 (1995)), respectively; lane 8, 100 nM CMH-1; lane 9, 10 units/ml granzyme B; and M, molecular weight markers in kDa.

**Fig. 1C** ICE cleavage converts inactive pro-IGIF to active IGIF which induces IFN- $\gamma$  production in Th1 helper cells. Uncleaved (Pro-IGIF), ICE-cleaved (Pro-IGIF/ICE), CPP32-cleaved (Pro-IGIF/ CPP32), and recombinant mature IGIF (rIGIF) were incubated with



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A.E7 Th1 cells at 12 ng/ml (open bar) and 120 ng/ml (hatched bar) for eighteen hours and the levels of IFN- $\gamma$  released into the culture medium assayed by ELISA (Example 23). A.E7 cells cultured with buffer, ICE alone (ICE) or CPP32 alone (CPP32) were assayed similarly for negative controls. The numbers represent the average of three determinations.

**Fig. 2A** Mature IGIF (18-kDa) is produced by Cos cells co-transfected with pro-IGIF and ICE-expressing plasmids. Cell lysates (left) and conditioned medium (right) from Cos cells transfected with a pro-IGIF expression plasmid in the absence (-) or presence of an expression plasmid encoding wild type (ICE) or inactive mutant (ICE-C285S) ICE. Transfected cells were metabolically labeled with  $^{35}\text{S}$ -methionine, proteins from cell lysates and conditioned medium immunoprecipitated with anti-IGIF antisera and separated by SDS-PAGE (Example 24). Mobilities of pro-IGIF and the 18-kDa mature IGIF are indicated on the right. Molecular weight markers in kDa are shown on the left.

**Fig. 2B** IFN- $\gamma$  inducing activity is detected in Cos cells co-transfected with pro-IGIF and ICE-expressing plasmids. Cell lysates (hatched bar) and conditioned medium (open bar) from Cos cells transfected with a pro-IGIF expression plasmid in the absence (Pro-IGIF) or presence (Pro-IGIF/ICE) of an expression plasmid encoding wild type (ICE) were assayed for IFN- $\gamma$  levels (ng/ml) by ELISA. Cos cells transfected with buffer (Mock) or an ICE-expressing plasmid alone (ICE) served as negative controls (Example 24).

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**Fig. 3A** Kupffer cells from mice lacking ICE are defective in the export of IGIF. Kupffer cells from wild type mice (ICE +/+) or ICE-deficient mice homozygous for an ICE mutation (ICE -/-) were isolated and primed with LPS for three hours. The levels of immunoreactive IGIF polypeptides in the conditioned media (ng/ml) of wild type cells were measured by ELISA (Example 25). N.D. (not detectable) indicates that the IGIF concentration was less than 0.1 ng/ml.

**Fig. 3B** Kupffer cells from mice lacking ICE are defective in the export of mature IGIF. Kupffer cells from wild type mice (ICE +/+) or ICE deficient mice homozygous for an ICE mutation (ICE -/-) were isolated and primed with LPS for three hours. Primed cells were metabolically labeled with <sup>35</sup>S-methionine, proteins from cell lysates and conditioned medium immunoprecipitated with anti-IGIF antisera and separated by SDS-PAGE (Example 25). Mobilities of pro-IGIF and the 18-kDa mature IGIF are indicated on the right. Molecular mass markers in kDa are shown on the left.

**Fig. 3C** Serum from ICE-deficient mice contains reduced levels of IGIF. Serum samples from wild type mice (ICE +/+) or ICE deficient mice homozygous for an ICE mutation (ICE -/-) were assayed for IGIF levels (ng/ml) by ELISA (Example 25).

**Fig. 3D** Serum from ICE-deficient mice contains reduced levels of IFN- $\gamma$ . Serum samples from wild type mice (ICE +/+) or ICE deficient mice homozygous for an ICE mutation (ICE -/-) were assayed for IFN- $\gamma$  levels (ng/ml) by ELISA (Example 25).

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**Fig. 4** Serum IFN- $\gamma$  levels are significantly reduced in ICE-deficient mice after an acute challenge with LPS (Example 26). Serum samples from wild type mice (filled squares) or ICE-deficient mice (filled circles) were assayed for IFN- $\gamma$  levels (ng/ml) by ELISA as a function of time (hours) after LPS challenge. Temperatures of the animals during the time course in degrees Celcius is shown for wild type mice (open squares) or ICE-deficient mice (open circles).

**Fig. 5** The ICE inhibitor, AcYVAD-aldehyde (AcYVAD-CHO), inhibits LPS-stimulated IL-1 $\beta$  and IFN- $\gamma$  synthesis by human peripheral blood mononuclear cells (PBMC). Percent (%) inhibition as a function of inhibitor concentration ( $\mu$ M) is shown for IL-1 $\beta$  (open squares) and IFN- $\gamma$  (open diamonds) synthesis.

**Fig. 6** Compound **214e** inhibits IL-1 $\beta$  production in LPS-challenged mice. Serum samples from CD1 mice were assayed for IL-1 $\beta$  levels (pg/ml) by ELISA after LPS challenge. Compound **214e** was administered by intraperitoneal (IP) injection one hour after LPS challenge. Blood was collected seven hours after LPS challenge (see Example 7).

**Fig. 7** Compound **217e** inhibits IL-1 $\beta$  production in LPS-challenged mice. Serum samples from CD1 mice were assayed for IL-1 $\beta$  levels (pg/ml) by ELISA after LPS challenge. Compound **217e** was administered by intraperitoneal (IP) injection one hour after LPS challenge. Blood was collected seven hours after LPS challenge (see Example 7).

**Fig. 8** Compound **214e**, but not compound **217e**,

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inhibits IL-1 $\beta$  production in LPS-challenged mice when administered by oral gavage. This assay measures oral absorption under similar conditions as those described for Figs. 6 and 7. These results indicates that **214e** is potentially orally active as an ICE inhibitor (see Example 7).

**Fig. 9** Compound **214e** and analogs of **214e** also inhibit IL-1 $\beta$  production after IP administration. These results were obtained in the assay described for Figs. 6 and 7 and Example 7.

**Fig. 10** Compound **214e**, and analogs of **214e**, also inhibit IL-1 $\beta$  production after oral (PO) administration. These results were obtained in the assay described for Figs. 6 and 7 and Example 7.

**Figs. 11A/B** Compounds **302** and **304a** show detectable blood levels when administered orally (50mg/kg, in 0.5 % carboxymethylcellulose) to mice. Blood samples were collected at 1 and 7 hours after dosing. Compounds **302** and **304a** are prodrugs of **214e** and are metabolized to **214e** *in vivo*. Compound **214e** shows no blood levels above 0.10  $\mu$ g/ml when administered orally (Example 8).

**Fig. 12** Compound **412f** blocks the progression of type II collagen-induced arthritis in male DBA/1J mice (Wooley, P.H., Methods in Enzymology, 162, pp. 361-373 (1988) and Geiger, T., Clinical and Experimental Rheumatology, 11, pp. 515-522 (1993)). Compound **412f** was administered twice a day (10, 25 and 50mg/kg), approximately 7h apart, by oral gavage. Inflammation was measured on the Arthritis Severity Score on a 1 to 4 scale of increasing severity. The scores of the two front paws were added to give the final score (see Example 21).

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**Fig. 13** Compound 412d blocks the progression of type II collagen-induced arthritis in male DBA/1J mice. The results were obtained as described for **Fig. 12** and in Example 21.

5 **Fig. 14** Compound 696a blocks the progression of type II collagen-induced arthritis in male DBA/1J mice. The results were obtained as described for **Fig. 12** and in Example 21.

#### ABBREVIATIONS AND DEFINITIONS

10	<u>Abbreviations</u>	
	<u>Designation</u>	<u>Reagent or Fragment</u>
	Ala	alanine
	Arg	arginine
	Asn	asparagine
15	Asp	aspartic acid
	Cys	cysteine
	Gln	glutamine
	Glu	glutamic acid
	Gly	glycine
20	His	histidine
	Ile	isoleucine
	Leu	leucine
	Lys	lysine
	Met	methionine
25	Phe	phenylalanine
	Pro	proline
	Ser	serine
	Thr	threonine
	Trp	tryptophan
30	Tyr	tyrosine
	Val	valine
	Ac <sub>2</sub> O	acetic anhydride
	n-Bu	normal-butyl

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	DMF	dimethylformamide
	DIEA	<i>N,N</i> -diisopropylethylamine
	EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
5	Et <sub>2</sub> O	diethyl ether
	EtOAc	ethyl acetate
	Fmoc	9-fluorenylmethoxycarbonyl
	HBTU	O-benzotriazol-1-yl- <i>N,N,N',N'</i> -tetramethyluronium
10		hexafluorophosphate
	HOBT	1-hydroxybenzotriazole hydrate
	MeOH	methanol
	TFA	trifluoroacetic acid
	Alloc	allyloxycarbonyl
15		

### Definitions

The following terms are employed herein:

The term "interferon gamma inducing factor" or "IGIF" refers to a factor which is capable of stimulating the endogenous production of IFN- $\gamma$ .

The term "ICE inhibitor" refers to a compound which is capable of inhibiting the ICE enzyme. ICE inhibition may be determined using the methods described and incorporated by reference herein. The skilled practitioner realizes that an in vivo ICE inhibitor is not necessarily an in vitro ICE inhibitor. For example, a prodrug form of a compound typically demonstrates little or no activity in in vitro assays. Such prodrug forms may be altered by metabolic or other biochemical processes in the patient to provide an in vivo ICE inhibitor.

The term "cytokine" refers to a molecule which mediates interactions between cells.

The term "condition" refers to any disease,

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disorder or effect that produces deleterious biological consequences in a subject.

The term "subject" refers to an animal, or to one or more cells derived from an animal. Preferably, the animal is a mammal, most preferably a human. Cells may be in any form, including but not limited to cells retained in tissue, cell clusters, immortalized cells, transfected or transformed cells, and cells derived from an animal that have been physically or phenotypically altered.

The term "active site" refers to any or all of the following sites in ICE: the substrate binding site, the site where an inhibitor binds and the site where the cleavage of substrate occurs.

The term "heterocycle" or "heterocyclic" refers to a stable mono- or polycyclic compound which may optionally contain one or two double bonds or may optionally contain one or more aromatic rings. Each heterocycle consists of carbon atoms and from one to four heteroatoms independently selected from a group including nitrogen, oxygen, and sulfur. As used herein, the terms "nitrogen heteroatoms" and "sulphur heteroatoms" include any oxidized form of nitrogen or sulfur and the quaternized form of any basic nitrogen. Heterocycles defined above include, for example, pyrimidinyl, tetrahydroquinolyl, tetrahydroisoquinolinyl, purinyl, pyrimidyl, indolinyl, benzimidazolyl, imidazolyl, imidazolinoyl, imidazolidinyl, quinolyl, isoquinolyl, indolyl, pyridyl, pyrrolyl, pyrrolinyl, pyrazolyl, pyrazinyl, quinoxolyl, piperidinyl, morpholinyl, thiamorpholinyl, furyl, thienyl, triazolyl, thiazolyl,  $\beta$ -carbolinyl, tetrazolyl, thiazolidinyl, benzofuranoyl, thiamorpholinyl sulfone, benzoxazolyl, oxopiperidinyl, oxopyrroldinyl, oxoazepinyl, azepinyl, isoxazolyl,

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tetrahydropyranyl, tetrahydrofuranyl, thiadiazolyl, benzodioxolyl, benzothienyl, tetrahydrothiophenyl and sulfolanyl. Further heterocycles are described in A.R. Katritzky and C.W. Rees, eds., Comprehensive Heterocyclic Chemistry: The Structure, Reactions, Synthesis and Use of Heterocyclic Compounds, Vol. 1-8, Pergamon Press, NY (1984).

The term "cycloalkyl" refers to a mono- or polycyclic group which contains 3 to 15 carbons and may optionally contain one or two double bonds. Examples include cyclohexyl, adamantyl and norbornyl.

The term "aryl" refers to a mono- or polycyclic group which contains 6, 10, 12, or 14 carbons in which at least one ring is aromatic. Examples include phenyl, naphthyl, and tetrahydronaphthalene.

The term "heteroaromatic" refers to a mono- or polycyclic group which contains 1 to 15 carbon atoms and from 1 to 4 heteroatoms, each of which is selected independently from a group including sulphur, nitrogen and oxygen, and which additionally contains from 1 to 3 five or six membered rings, at least one of which is aromatic.

The term "alpha-amino acid" ( $\alpha$ -amino acid) refers to both the naturally occurring amino acids and other "non-protein"  $\alpha$ -amino acids commonly utilized by those in the peptide chemistry arts when preparing synthetic analogues of naturally occurring peptides, including D and L forms. The naturally occurring amino acids are glycine, alanine, valine, leucine, isoleucine, serine, methionine, threonine, phenylalanine, tyrosine, tryptophan, cysteine, proline, histidine, aspartic acid, asparagine, glutamic acid, glutamine,  $\gamma$ -carboxyglutamic acid, arginine, ornithine and lysine. Examples of "non-protein" alpha-amino acids include



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hydroxylysine, homoserine, homotyrosine, homo-phenylalanine, citrulline, kynurenine, 4-amino-phenylalanine, 3-(2-naphthyl)-alanine, 3-(1-naphthyl)-alanine, methionine sulfone, t-butyl-alanine,

5 t-butylglycine, 4-hydroxyphenylglycine, aminoalanine, phenylglycine, vinylalanine, propargyl-glycine, 1,2,4-triazolo-3-alanine, 4,4,4-trifluoro-threonine, thyronine, 6-hydroxytryptophan, 5-hydro-xytryptophan, 3-hydroxykynurenine, 3-aminotyrosine, trifluoromethyl-

10 alanine, 2-thienylalanine, (2-(4-pyridyl)ethyl)-cysteine, 3,4-dimethoxy-phenylalanine, 3-(2-thiazolyl)-alanine, ibotenic acid, 1-amino-1-cyclopentane-carboxylic acid, 1-amino-1-cyclohexanecarboxylic acid, quisqualic acid, 3-trifluoromethylphenylalanine,

15 4-trifluoro-methylphenylalanine, cyclohexylalanine, cyclo-hexylglycine, thiohistidine, 3-methoxytyrosine, elastatinal, norleucine, norvaline, allose, alloisoleucine, homoarginine, thioproline, dehydroproline, hydroxy-proline, isonipectotic acid, homoproline, cyclohexyl-

20 glycine,  $\alpha$ -amino-n-butyric acid, cyclohexylalanine, aminophenylbutyric acid, phenylalanines substituted at the ortho, meta, or para position of the phenyl moiety with one or two of the following: a (C<sub>1</sub>-C<sub>4</sub>) alkyl, a (C<sub>1</sub>-C<sub>4</sub>) alkoxy, halogen or nitro groups or substituted

25 with a methylenedioxy group;  $\beta$ -2- and 3-thienyl-alanine,  $\beta$ -2- and 3-furanylalanine,  $\beta$ -2-, 3- and 4-pyridylalanine,  $\beta$ -(benzothienyl-2- and 3-yl)alanine,  $\beta$ -(1- and 2-naphthyl)alanine, O-alkylated derivatives of serine, threonine or tyrosine, S-alkylated cysteine,

30 S-alkylated homocysteine, O-sulfate, O-phosphate and O-carboxylate esters of tyrosine, 3-sulfo-tyrosine, 3-carboxy-tyrosine, 3-phospho-tyrosine, 4-methane sulfonic acid ester of tyrosine, 4-methane phosphonic acid ester of tyrosine, 3,5-diiodotyrosine, 3-nitro-

35 tyrosine,  $\epsilon$ -alkyl lysine, and delta-alkyl ornithine.

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Any of these  $\alpha$ -amino acids may be substituted with a methyl group at the alpha position, a halogen at any aromatic residue on the  $\alpha$ -amino side chain, or an appropriate protective group at the O, N, or S atoms of the side chain residues. Appropriate protective groups are disclosed in "Protective Groups In Organic Synthesis," T.W. Greene and P.G.M. Wuts, J. Wiley & Sons, NY, NY, 1991.

The term "substitute" refers to the replacement of a hydrogen atom in a compound with a substituent group. In the present invention, those hydrogen atoms which form a part of a hydrogen bonding moiety which is capable of forming a hydrogen bond with the carbonyl oxygen of Arg-341 of ICE or the carbonyl oxygen of Ser-339 of ICE are excluded from substitution. These excluded hydrogen atoms include those which comprise an -NH- group which is alpha to a -CO- group and are depicted as -NH- rather than an X group or some other designation in the following diagrams: (a) through (t), (v) through (z).

The term "straight chain" refers to a contiguous unbranching string of covalently bound atoms. The straight chain may be substituted, but these substituents are not a part of the straight chain.

The term " $K_i$ " refers to a numerical measure of the effectiveness of a compound in inhibiting the activity of a target enzyme such as ICE. Lower values of  $K_i$  reflect higher effectiveness. The  $K_i$  value is a derived by fitting experimentally determined rate data to standard enzyme kinetic equations (see I. H. Segel, Enzyme Kinetics, Wiley-Interscience, 1975).

The term "patient" as used in this application refers to any mammal, especially humans.

The term "pharmaceutically effective amount" refers to an amount effective in treating or

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ameliorating an IL-1-, apoptosis-, IGIF- or IFN- $\gamma$ -mediated disease in a patient. The term "prophylactically effective amount" refers to an amount effective in preventing or substantially lessening

5 IL-1-, apoptosis-, IGIF or IFN- $\gamma$  mediated diseases in a patient.

The term "pharmaceutically acceptable carrier or adjuvant" refers to a non-toxic carrier or adjuvant that may be administered to a patient, together with a

10 compound of this invention, and which does not destroy the pharmacological activity thereof.

The term "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, ester, or salt of such ester, of a compound of this

15 invention or any other compound which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention or an anti-ICE active metabolite or residue thereof.

Pharmaceutically acceptable salts of the

20 compounds of this invention include, for example, those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic,

25 lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable,

30 may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts. Salts derived from appropriate bases include alkali metal (e.g., sodium), alkaline earth

35 metal (e.g., magnesium), ammonium and N-(C<sub>1-4</sub> alkyl)<sub>4</sub><sup>+</sup>

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salts.

This invention also envisions the "quaternization" of any basic nitrogen-containing groups of the compounds disclosed herein. The basic nitrogen can be quaternized with any agents known to those of ordinary skill in the art including, for example, lower alkyl halides, such as methyl, ethyl, propyl and butyl chloride, bromides and iodides; dialkyl sulfates including dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; and aralkyl halides including benzyl and phenethyl bromides. Water or oil-soluble or dispersible products may be obtained by such quaternization.

The ICE inhibitors of this invention may contain one or more "asymmetric" carbon atoms and thus may occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be of the R or S configuration. Although specific compounds and scaffolds exemplified in this application may be depicted in a particular stereochemical configuration, compounds and scaffolds having either the opposite stereochemistry at any given chiral center or mixtures thereof are also envisioned.

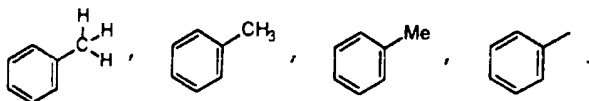
The ICE inhibitors of this invention may comprise ring structures which may optionally be substituted at carbon, nitrogen or other atoms by various substituents. Such ring structures may be singly or multiply substituted. Preferably, the ring structures contain between 0 and 3 substituents. When multiply substituted, each substituent may be picked independently of any other substituent as long as the

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combination of substituents results in the formation of a stable compound.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and administration to a mammal by methods known in the art. Typically, such compounds are stable at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

Substituents may be represented in various forms. These various forms are known to the skilled practitioner and may be used interchangeably. For example, a methyl substituent on a phenyl ring may be represented in any of the following forms:



Various forms of substituents such as methyl are used herein interchangeably.

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#### DETAILED DESCRIPTION OF THE INVENTION

In order that the invention herein described may be more fully understood, the following detailed description is set forth.

The ICE inhibitors of one embodiment (A) of this invention are those of formula  $\alpha$ :



wherein:

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$X_1$  is -CH;

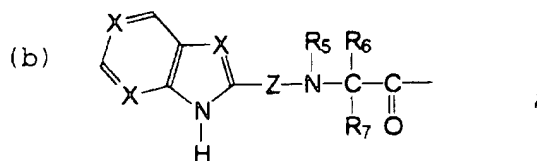
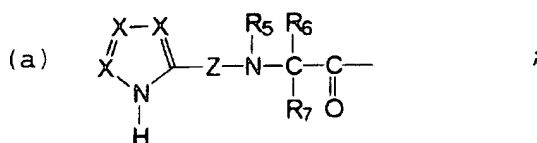
$g$  is 0 or 1;

each  $J$  is independently selected from the group consisting of -H, -OH, and -F, provided that when a first and second  $J$  are bound to a C and said first  $J$  is -OH, said second  $J$  is -H;

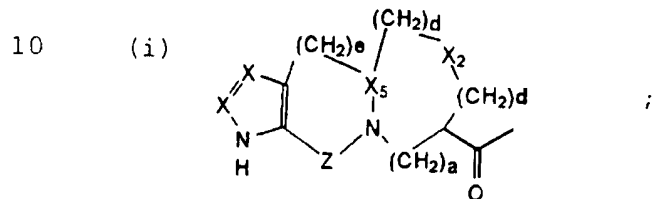
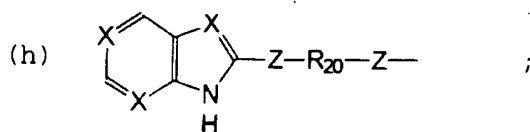
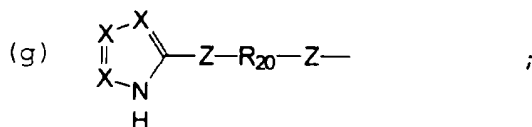
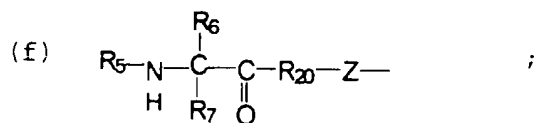
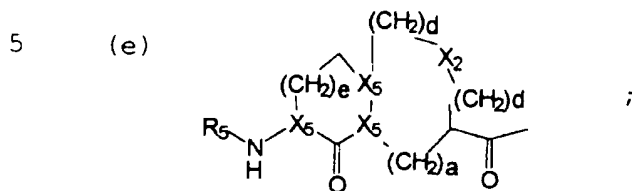
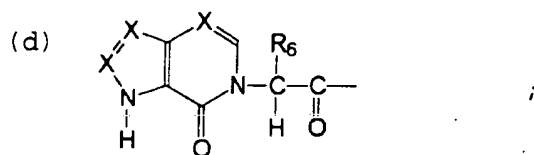
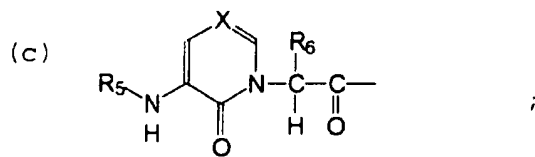
$m$  is 0, 1, or 2;

$T$  is -OH, -CO-CO<sub>2</sub>H, -CO<sub>2</sub>H, or any bioisosteric replacement for -CO<sub>2</sub>H;

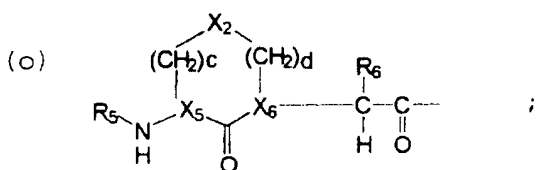
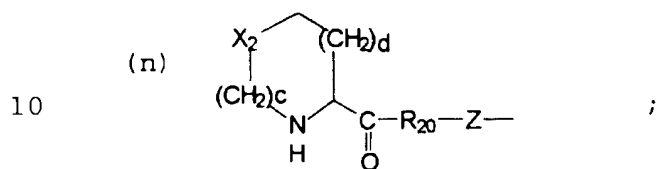
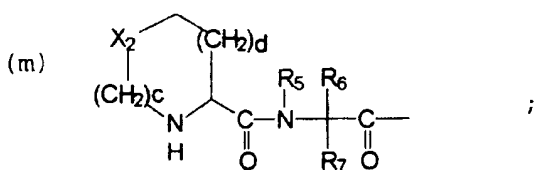
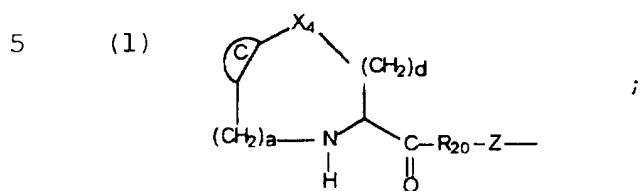
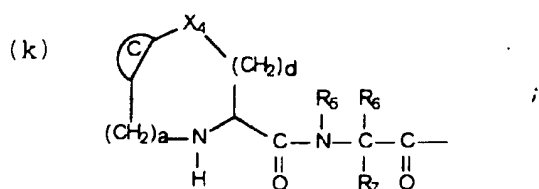
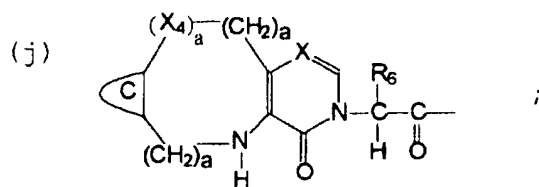
$R_1$  is selected from the group consisting of the following formulae, in which any ring may optionally be singly or multiply substituted at any carbon by  $Q_1$ , at any nitrogen by  $R_5$ , or at any atom by =O, -OH, -CO<sub>2</sub>H, or halogen; any saturated ring may optionally be unsaturated at one or two bonds; and wherein  $R_1$  (e) and  $R_1$  (y) are optionally benzofused;



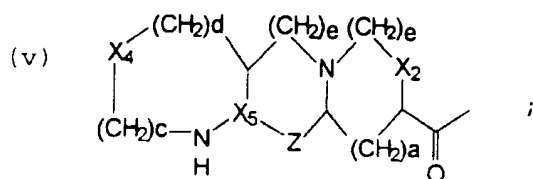
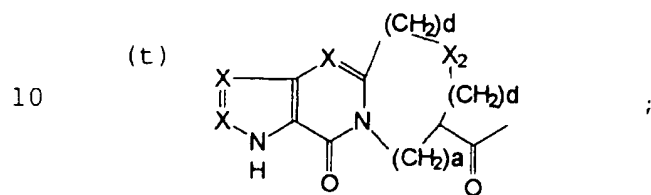
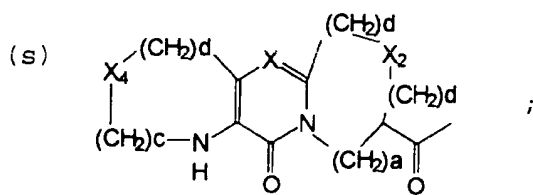
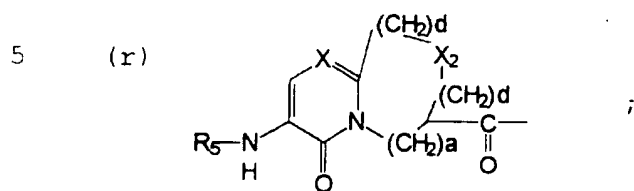
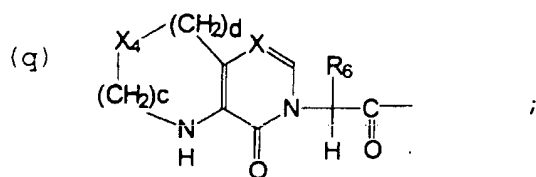
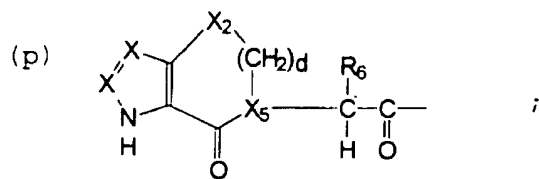
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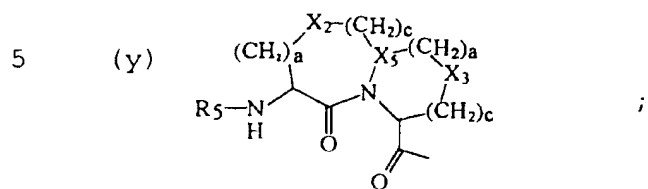
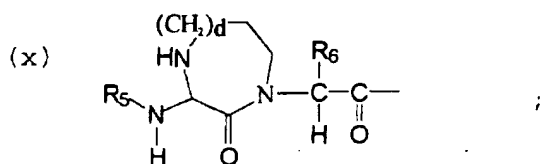
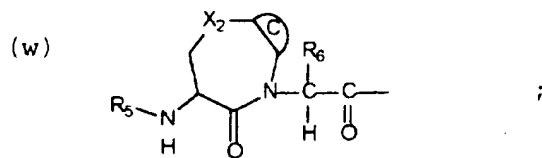
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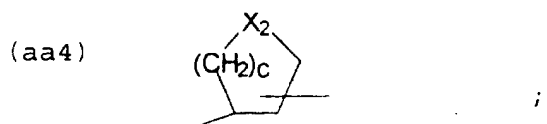
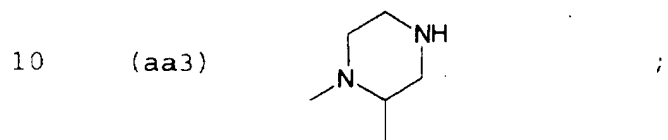
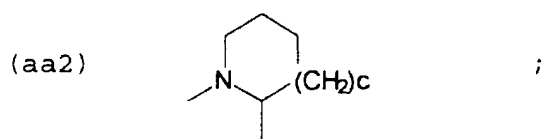
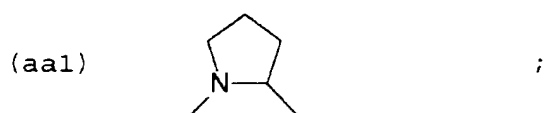




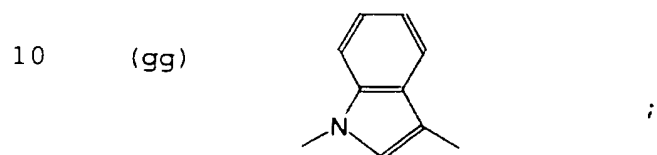
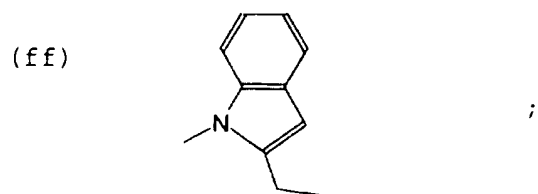
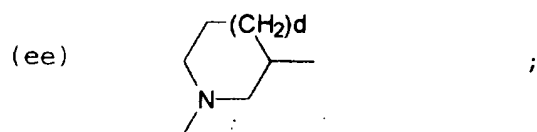
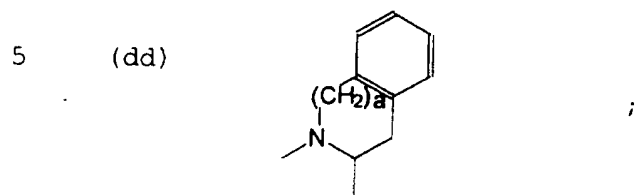
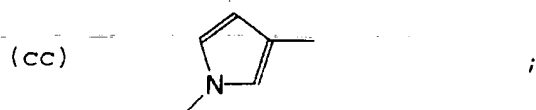
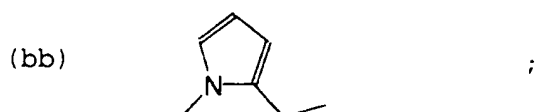
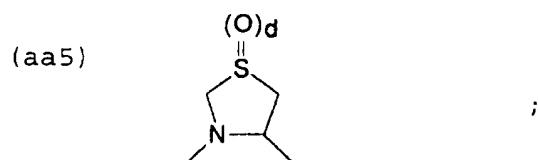
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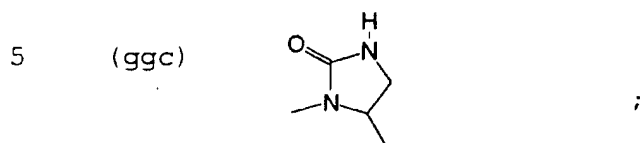
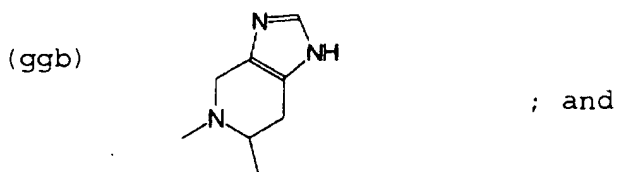
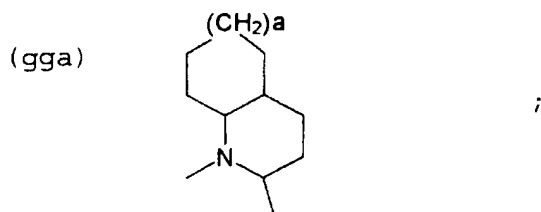
$R_{20}$  is selected from the group consisting of:



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- 30 -



wherein each ring C is independently chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

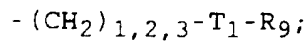
R<sub>3</sub> is:

- CN,
- CH=CH-R<sub>9</sub>,
- CH=N-O-R<sub>9</sub>,
- 15 -(CH<sub>2</sub>)<sub>1-3</sub>-T<sub>1</sub>-R<sub>9</sub>,
- CJ<sub>2</sub>-R<sub>9</sub>,
- CO-R<sub>13</sub>, or
- /R<sub>5</sub>
- CO-CO-N
- 20 \R<sub>10</sub>;

each R<sub>4</sub> is independently selected from the group consisting of:

- H,
- Ar<sub>1</sub>,
- 25 -R<sub>9</sub>,
- T<sub>1</sub>-R<sub>9</sub>, and

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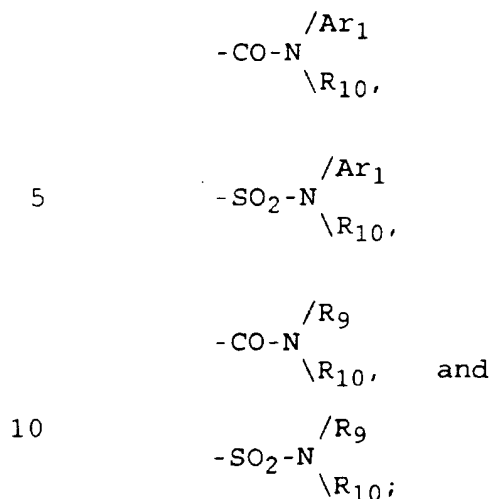
each  $\text{T}_1$  is independently selected from the group consisting of:

- CH=CH-,
- 5        -O-,
- S-,
- SO-,
- SO<sub>2</sub>-,
- NR<sub>10</sub>-,
- 10       -NR<sub>10</sub>-CO-,
- CO-,
- O-CO-,
- CO-O-,
- CO-NR<sub>10</sub>-,
- 15       -O-CO-NR<sub>10</sub>-,
- NR<sub>10</sub>-CO-O-,
- NR<sub>10</sub>-CO-NR<sub>10</sub>-,
- SO<sub>2</sub>-NR<sub>10</sub>-,
- NR<sub>10</sub>-SO<sub>2</sub>-,        and
- 20       -NR<sub>10</sub>-SO<sub>2</sub>-NR<sub>10</sub>-;

each  $\text{R}_5$  is independently selected from the group consisting of:

- H,
- Ar<sub>1</sub>,
- 25       -CO-Ar<sub>1</sub>,
- SO<sub>2</sub>-Ar<sub>1</sub>,
- CO-NH<sub>2</sub>,
- SO<sub>2</sub>-NH<sub>2</sub>,
- R<sub>9</sub>,
- 30       -CO-R<sub>9</sub>,
- CO-O-R<sub>9</sub>,
- SO<sub>2</sub>-R<sub>9</sub>,

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R<sub>6</sub> and R<sub>7</sub> taken together form a saturated 4-8 member carbocyclic ring or heterocyclic ring containing  
 15 -O-, -S-, or -NH-; or R<sub>7</sub> is -H and R<sub>6</sub> is  
 -H  
 -Ar<sub>1</sub>,  
 -R<sub>9</sub>,  
 -(CH<sub>2</sub>)<sub>1,2,3</sub>-T<sub>1</sub>-R<sub>9</sub>, or  
 20 an α-amino acid side chain residue;

each R<sub>9</sub> is a C<sub>1-6</sub> straight or branched alkyl group optionally singly or multiply substituted with -OH, -F, or =O and optionally substituted with one or two Ar<sub>1</sub> groups;

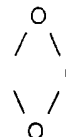
25 each R<sub>10</sub> is independently selected from the group consisting of -H or a C<sub>1-6</sub> straight or branched alkyl group;

each R<sub>13</sub> is independently selected from the group consisting of -Ar<sub>2</sub>, -R<sub>4</sub> and -N-OH  
 30  $\begin{array}{c} \text{\R}_5; \end{array}$

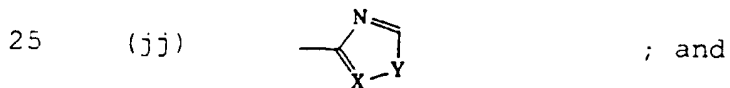
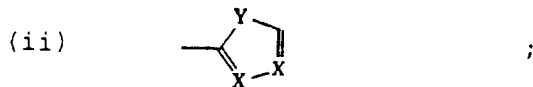
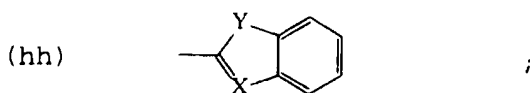
each Ar<sub>1</sub> is a cyclic group independently selected

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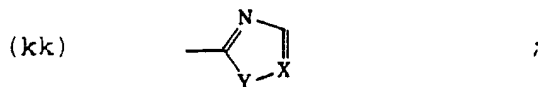
from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 15 carbon atoms and between 1 and 3 rings, said  
 5 cycloalkyl group being optionally benzofused, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocycle group containing at least one heteroatom group selected from -O-, -S-, -SO-, -SO<sub>2</sub>-, =N-, and -NH-, said heterocycle  
 10 group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted with -NH<sub>2</sub>, -CO<sub>2</sub>H, -Cl, -F, -Br, -I, -NO<sub>2</sub>, -CN,

15 =O, -OH, -perfluoro C<sub>1-3</sub> alkyl,  CH<sub>2</sub>, or -Q<sub>1</sub>;

20 each Ar<sub>2</sub> is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by -Q<sub>1</sub> and -Q<sub>2</sub>:



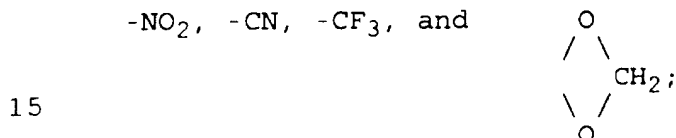
- 34 -



each  $Q_1$  is independently selected from the group consisting of:

- 5        -Ar<sub>1</sub>  
        -O-Ar<sub>1</sub>  
        -R<sub>9</sub>,  
        -T<sub>1</sub>-R<sub>9</sub>,                      and  
        -(CH<sub>2</sub>)<sub>1,2,3</sub>-T<sub>1</sub>-R<sub>9</sub>;

10        each  $Q_2$  is independently selected from the group consisting of -OH, -NH<sub>2</sub>, -CO<sub>2</sub>H, -Cl, -F, -Br, -I, -NO<sub>2</sub>, -CN, -CF<sub>3</sub>, and



provided that when -Ar<sub>1</sub> is substituted with a  $Q_1$  group which comprises one or more additional -Ar<sub>1</sub> groups, said additional -Ar<sub>1</sub> groups are not substituted with  $Q_1$ ;

20

each X is independently selected from the group consisting of =N-, and =CH-;

each X<sub>2</sub> is independently selected from the group consisting of -O-, -CH<sub>2</sub>-, -NH-, -S-, -SO-, and -SO<sub>2</sub>-;

25        each X<sub>3</sub> is independently selected from the group consisting of -CH<sub>2</sub>-, -S-, -SO-, and -SO<sub>2</sub>-;

each X<sub>4</sub> is independently selected from the group consisting of -CH<sub>2</sub>- and -NH-;



- 35 -

each  $X_5$  is independently selected from the group  
consisting of  $\begin{array}{c} \text{-CH-} \\ | \end{array}$  and  $\begin{array}{c} \text{-N-} \\ | \end{array}$ ;

$X_6$  is  $\text{-CH-}$  or  $\text{-N-}$ ;

5 each  $Y$  is independently selected from the group  
consisting of  $\text{-O-}$ ,  $\text{-S-}$ , and  $\text{-NH}$ ;

each  $Z$  is independently  $\text{CO}$  or  $\text{SO}_2$ ;

each  $a$  is independently 0 or 1;

each  $c$  is independently 1 or 2;

10 each  $d$  is independently 0, 1, or 2; and

each  $e$  is independently 0, 1, 2, or 3;

provided that when

$R_1$  is (f),

15  $R_6$  is an  $\alpha$ -amino acid side chain residue, and

$R_7$  is  $\text{-H}$ ,

then (aa1) and (aa2) must be substituted with  $Q_1$ ;

also provided that when

20  $R_1$  is (o),

$g$  is 0,

$J$  is  $\text{-H}$ ,

$m$  is 1,

$R_6$  is an  $\alpha$ -amino acid side chain residue,

25  $R_7$  is  $\text{-H}$ ,

$X_2$  is  $\text{-CH}_2\text{-}$ ,

$X_5$  is  $\begin{array}{c} \text{-CH-} \\ | \end{array}$ ,

30  $X_6$  is  $\begin{array}{c} \text{-N-} \\ | \end{array}$ , and

$R_3$  is  $\begin{array}{c} \text{-CO-N} \\ \text{ } \end{array} \begin{array}{c} /R_{10} \\ \backslash R_{10} \end{array}$ , or  $\text{-CO-R}_{13}$ , when

- 36 -

R<sub>13</sub> is:

- 5
- CH<sub>2</sub>-O-CO-Ar<sub>1</sub>,
  - CH<sub>2</sub>-S-CO-Ar<sub>1</sub>,
  - CH<sub>2</sub>-O-Ar<sub>1</sub>,
  - CH<sub>2</sub>-S-Ar<sub>1</sub>, or
  - R<sub>4</sub> when -R<sub>4</sub> is -H;

then the ring of the R<sub>1</sub>(o) group must be substituted with Q<sub>1</sub> or benzofused; and

provided that when

- 10
- R<sub>1</sub> is (w),
  - g is 0,
  - J is -H,
  - m is 1,
  - T is -CO<sub>2</sub>H,
  - 15 X<sub>2</sub> is O,
  - R<sub>5</sub> is benzyloxycarbonyl, and
  - ring C is benzo,

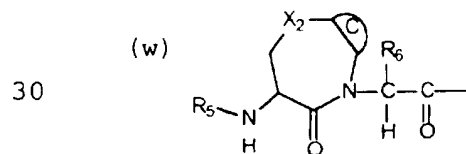
then R<sub>3</sub> cannot be -CO-R<sub>13</sub> when:

- 20
- R<sub>13</sub> is -CH<sub>2</sub>-O-Ar<sub>1</sub> and
  - Ar<sub>1</sub> is 1-phenyl-3-trifluoromethyl-pyrazole-5-yl wherein the phenyl is optionally substituted with a chlorine atom;

or when

- 25
- R<sub>13</sub> is -CH<sub>2</sub>-O-CO-Ar<sub>1</sub>, wherein
  - Ar<sub>1</sub> is 2,6-dichlorophenyl.

Preferred compounds of embodiment A employ formula α, wherein R<sub>1</sub> is (w):

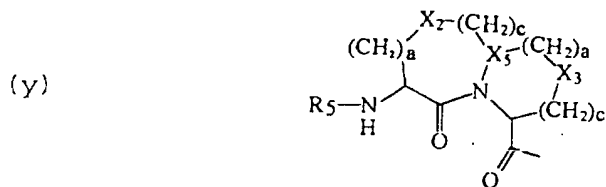


wherein the other substituents are as described

- 37 -

above.

Other preferred compounds of embodiment A employ formula  $\alpha$ , wherein  $R_1$  is (y):



5 wherein the other substituents are as described above.

More preferred compounds of embodiment A employ formula  $\alpha$ , wherein:

$X_1$  is -CH;

10 g is 0;

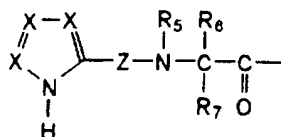
J is -H;

m is 0 or 1 and T is -CO-CO<sub>2</sub>H, or any bioisosteric replacement for -CO<sub>2</sub>H, or

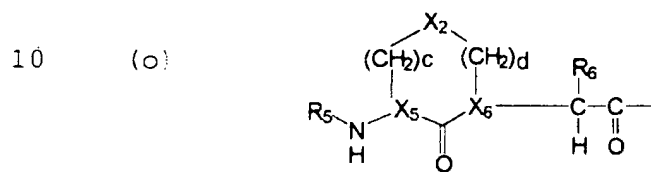
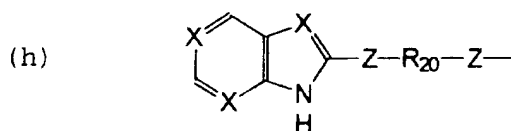
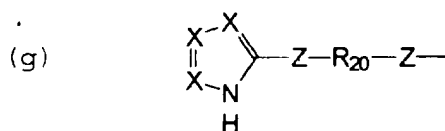
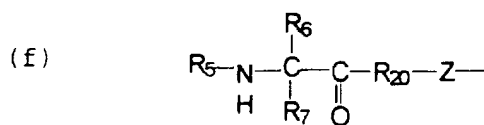
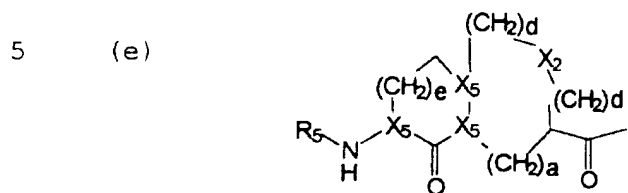
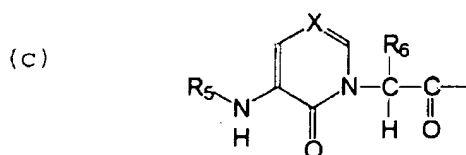
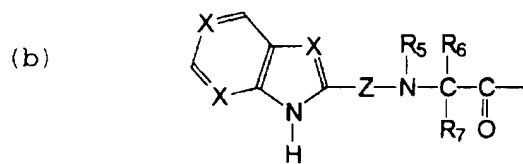
m is 1 and T is -CO<sub>2</sub>H;

15  $R_1$  is selected from the group consisting of the following formulae, in which any ring may optionally be singly or multiply substituted at any carbon by  $Q_1$ , at any nitrogen by  $R_5$ , or at any atom by =O, -OH, -CO<sub>2</sub>H, or halogen, and wherein (e) is optionally benzofused:

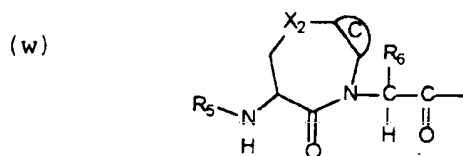
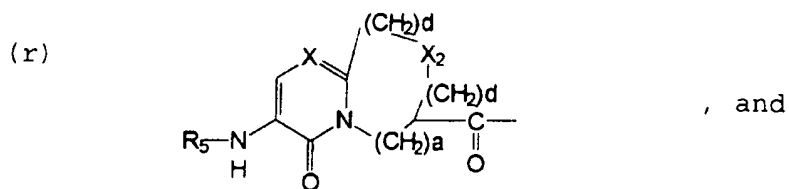
20 (a)



- 38 -

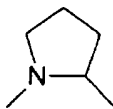


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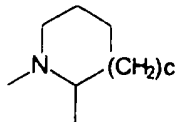


5  $R_{20}$  is:

(aa1)



(aa2)



and c is 1;

10 ring C is benzo optionally substituted with  
-C<sub>1-3</sub> alkyl, -O-C<sub>1-3</sub> alkyl, -Cl, -F or -CF<sub>3</sub>;

when R<sub>1</sub> is (a) or (b), R<sub>5</sub> is preferably -H, and

15 when R<sub>1</sub> is (c), (e), (f), (o), (r), (w), (x) or  
(y), R<sub>5</sub> is preferably:

-CO-Ar<sub>1</sub>  
-SO<sub>2</sub>-Ar<sub>1</sub>,  
-CO-NH<sub>2</sub>,  
-CO-NH-Ar<sub>1</sub>  
20 -CO-R<sub>9</sub>,  
-CO-O-R<sub>9</sub>,

- 40 -

-SO<sub>2</sub>-R<sub>9</sub>, or  
 -CO-NH-R<sub>9</sub>,

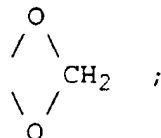
R<sub>7</sub> is -H and R<sub>6</sub> is: -H,  
 -R<sub>9</sub>, or  
 -Ar<sub>1</sub>;

5

R<sub>9</sub> is a C<sub>1-6</sub> straight or branched alkyl group  
 optionally substituted with =O and optionally  
 substituted with -Ar<sub>1</sub>;

10 R<sub>10</sub> is -H or a -C<sub>1-3</sub> straight or branched alkyl  
 group;

Ar<sub>1</sub> is phenyl, naphthyl, pyridyl, benzothiazolyl,  
 thienyl, benzothienyl, benzoxazolyl, 2-indanyl, or  
 indolyl optionally substituted with -O-C<sub>1-3</sub> alkyl, -NH-  
 C<sub>1-3</sub> alkyl, -N-(C<sub>1-3</sub> alkyl)<sub>2</sub>, -Cl, -F, -CF<sub>3</sub>,  
 15 -C<sub>1-3</sub> alkyl, or



20 Q<sub>1</sub> is R<sub>9</sub> or -(CH<sub>2</sub>)<sub>0,1,2</sub>-T<sub>1</sub>-(CH<sub>2</sub>)<sub>0,1,2</sub>-Ar<sub>1</sub>, wherein  
 T<sub>1</sub> is -O- or -S-;

each X is independently selected from the group  
 consisting of =N-, and =CH-;

25 each X<sub>2</sub> is independently selected from the group  
 consisting of -O-, -CH<sub>2</sub>-, -NH-, -S-, -SO-, and -SO<sub>2</sub>-;

each X<sub>5</sub> is independently selected from the group  
 consisting of -CH- and -N-;

30 X<sub>6</sub> is -CH- or -N-,

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provided that when:

$R_1$  is (o),

$X_2$  is  $-\text{CH}_2-$ ,

5  $X_5$  is  $-\text{CH}-$ , and  
 $\quad \quad \quad |$

$X_6$  is  $-\text{N}-$ ,  
 $\quad \quad \quad |$

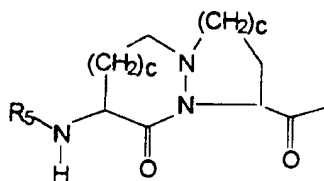
10 then the ring of the  $R_1(o)$  group must be  
substituted with  $Q_1$  or benzofused; and

$Z$  is  $\text{C}=\text{O}$ .

Most preferably, compounds of this more  
preferred embodiment are those wherein the  $R_1$  group is:

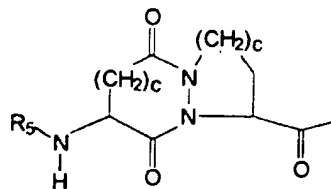
(e1)

15



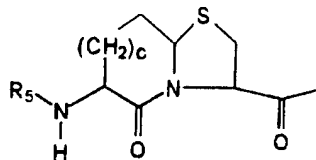
, or

(e2)



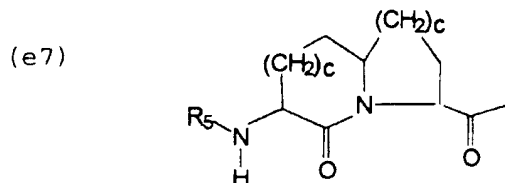
and  $c$  is 2; or

(e4)



, or

- 42 -



which is optionally benzofused,  
and c is 1 or 2;

provided that when R<sub>1</sub> is (e4),

5           g is 0,  
           J is -H,  
           m is 1,  
           T is -CO<sub>2</sub>H,  
           R<sub>5</sub> is benzyloxycarbonyl, and  
10          c is 1,

then R<sub>3</sub> cannot be -CO-R<sub>13</sub> when

R<sub>13</sub> is -CH<sub>2</sub>-O-Ar<sub>1</sub> and

Ar<sub>1</sub> is 1-phenyl-3-trifluoromethyl-pyrazole-  
5-yl, wherein the phenyl is optionally substituted with  
15       a chlorine atom; or when

R<sub>13</sub> is -CH<sub>2</sub>-O-CO-Ar<sub>1</sub>, wherein

Ar<sub>1</sub> is 2,6-dichlorophenyl,

and when the 2-position of the scaffold ring is  
20       substituted with para-fluoro-phenyl; and

also provided that when

R<sub>1</sub> is (e7),

g is 0,

J is -H,

25       m is 1,

T is -CO<sub>2</sub>H or -CO-NH-OH,

R<sub>5</sub> is a protective group for the N atom of an  
amino acid side chain residue, and  
each c is 1,



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then  $R_3$  cannot be  $-\text{CO}-R_{13}$  when

$R_{13}$  is:

$-\text{CH}_2-\text{O}-\text{CO}-\text{Ar}_1,$

$-\text{CH}_2-\text{S}-\text{CO}-\text{Ar}_1,$

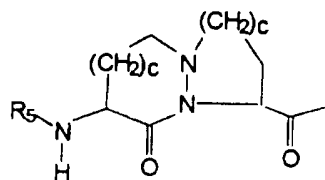
5  $-\text{CH}_2-\text{O}-\text{Ar}_1,$  or

$-\text{CH}_2-\text{S}-\text{Ar}_1.$

The most preferred compounds of this embodiment are those wherein:

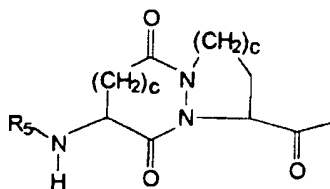
$R_1$  is:

10 (e1)



, or

(e2)



and  $c$  is 2;

$m$  is 1;

15  $T$  is  $-\text{CO}_2\text{H}$ ; and

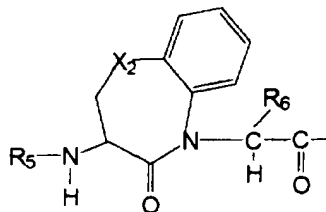
$R_3$  is  $-\text{CO}-R_{13}.$

Other most preferred compounds of this embodiment are those wherein:

$R_1$  is:

- 44 -

(w1)



; wherein

X<sub>2</sub> is:

-O- ,  
 -S- ,  
 -SO<sub>2</sub>-, or  
 -NH-;

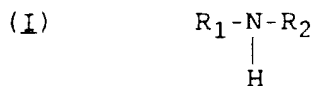
5

optionally substituted with R<sub>5</sub> or Q<sub>1</sub> at X<sub>2</sub> when X<sub>2</sub>  
 10 is -NH-; and

ring C is benzo substituted with -C<sub>1-3</sub> alkyl,  
 -O-C<sub>1-3</sub> alkyl, -Cl, -F or -CF<sub>3</sub>.

The ICE inhibitors of another embodiment (B)  
 of this invention are those of formula (I):

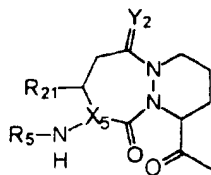
15



wherein:

R<sub>1</sub> is selected from the group consisting of the  
 20 following formulae:

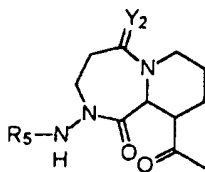
(e10)



;

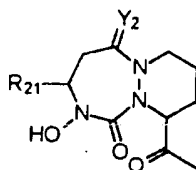
- 45 -

(e11)



;

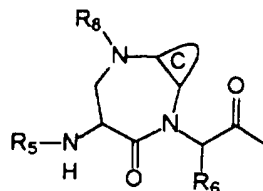
(e12)



;

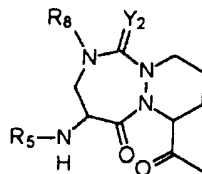
5

(w2)



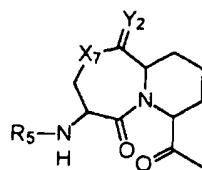
;

(y1)



;

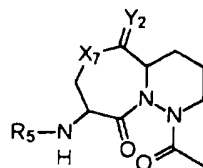
(y2)



;

10

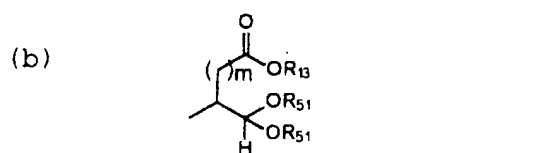
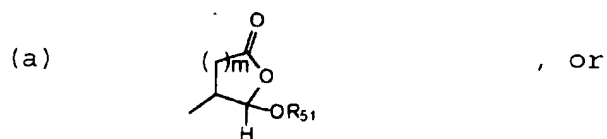
(z)



; and

ring C is chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

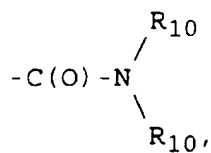
- 46 -

 $R_2$  is: $m$  is 1 or 2;

5

 $R_5$  is selected from the group consisting of:-C(O)- $R_{10}$ ,-C(O)O- $R_9$ ,

10

-S(O)<sub>2</sub>- $R_9$ ,

15

-C(O)-CH<sub>2</sub>-O- $R_9$ ,-C(O)C(O)- $R_{10}$ ,- $R_9$ ,

-H, and

-C(O)C(O)-OR<sub>10</sub>;

20

 $X_5$  is -CH- or -N-; $Y_2$  is H<sub>2</sub> or O; $X_7$  is -N( $R_8$ )- or -O-;

25

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R<sub>6</sub> is selected from the group consisting of -H and -CH<sub>3</sub>;

R<sub>8</sub> is selected from the group consisting of:

- 5                   -C(O)-R<sub>10</sub>,  
                  -C(O)O-R<sub>9</sub>,  
                  -C(O)-N(H)-R<sub>10</sub>,  
                  -S(O)<sub>2</sub>-R<sub>9</sub>,  
                  -S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
10                  -C(O)-CH<sub>2</sub>-OR<sub>10</sub>,  
                  -C(O)C(O)-R<sub>10</sub>;  
                  -C(O)-CH<sub>2</sub>N(R<sub>10</sub>)(R<sub>10</sub>),  
                  -C(O)-CH<sub>2</sub>C(O)-O-R<sub>9</sub>,  
                  -C(O)-CH<sub>2</sub>C(O)-R<sub>9</sub>,  
15                  -H, and  
                  -C(O)-C(O)-OR<sub>10</sub>;

20                  each R<sub>9</sub> is independently selected from the group consisting of -Ar<sub>3</sub> and a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, wherein the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

25                  each R<sub>10</sub> is independently selected from the group consisting of -H, -Ar<sub>3</sub>, a C<sub>3-6</sub> cycloalkyl group, and a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, wherein the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

R<sub>13</sub> is selected from the group consisting of H, Ar<sub>3</sub>, and a C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, -CONH<sub>2</sub>, -OR<sub>5</sub>, -OH, -OR<sub>9</sub>, or -CO<sub>2</sub>H;

- 48 -

each  $R_{51}$  is independently selected from the group consisting of  $R_9$ ,  $-C(O)-R_9$ ,  $-C(O)-N(H)-R_9$ , or each  $R_{51}$  taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing  $-O-$ ,  $-S-$ , or  $-NH-$ ;

5 each  $R_{21}$  is independently selected from the group consisting of  $-H$  or a  $-C_{1-6}$  straight or branched alkyl group;

each  $Ar_3$  is a cyclic group independently selected from the set consisting of an aryl group which contains  
 10 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from  $-O-$ ,  $-S-$ ,  $-SO-$ ,  $SO_2$ ,  $=N-$ , and  $-NH-$ ,  
 15 said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

20 each  $Q_1$  is independently selected from the group consisting of  $-NH_2$ ,  $-CO_2H$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-I$ ,  $-NO_2$ ,  $-CN$ ,  $=O$ ,  $-OH$ ,  $-perfluoro\ C_{1-3}\ alkyl$ ,  $R_5$ ,  $-OR_5$ ,  $-NHR_5$ ,  $OR_9$ ,  $-NHR_9$ ,  $R_9$ ,  $-C(O)-R_{10}$ , and



30 provided that when  $-Ar_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-Ar_3$  groups, said additional  $-Ar_3$  groups are not substituted with another  $-Ar_3$ .

- 49 -

Preferably,  $R_5$  is selected from the group consisting of:

- 5           - $C(O)-R_{10}$ ,  
           - $C(O)O-R_9$ , and  
           - $C(O)-NH-R_{10}$ .

Alternatively,  $R_5$  is selected from the group consisting of:

- 10           - $S(O)_2-R_9$ ,  
           - $S(O)_2-NH-R_{10}$ ,  
           - $C(O)-C(O)-R_{10}$ ,  
           - $R_9$ , and  
           - $C(O)-C(O)-OR_{10}$ .

More preferably:

$m$  is 1;

- 15            $R_{13}$  is H or a  $-C_{1-4}$  straight or branched alkyl group optionally substituted with  $-Ar_3$ ,  $-OH$ ,  $-OR_9$ , or  $-CO_2H$ , wherein the  $R_9$  is a  $-C_{1-4}$  branched or straight alkyl group, wherein  $Ar_3$  is morpholinyl or phenyl, wherein the phenyl is optionally substituted with  $Q_1$ ;

- 20            $R_{21}$  is  $-H$  or  $-CH_3$ ;

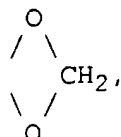
$R_{51}$  is a  $C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$ , wherein  $Ar_3$  is phenyl, optionally substituted by  $-Q_1$ ;

- 25            $Ar_3$  is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl;

- 50 -

each  $Q_1$  is independently selected from the group consisting of  $-NH_2$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-OH$ ,  $-R_9$ ,  $-NH-R_5$  wherein  $R_5$  is  $-C(O)-R_{10}$  or  $-S(O)_2-R_9$ ,  $-OR_5$  wherein  $R_5$  is  $-C(O)-R_{10}$ ,  $-OR_9$ ,  $-NHR_9$ , and

5

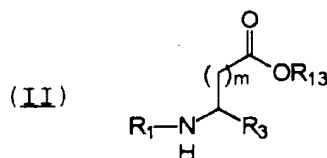


10 wherein each R<sub>9</sub> and R<sub>10</sub> are independently a -C<sub>1-6</sub>  
straight or branched alkyl group optionally substituted  
with Ar<sub>3</sub> wherein Ar<sub>3</sub> is phenyl;

provided that when  $-Ar_3$  is substituted with a  $Q_1$   
15 group which comprises one or more additional  $-Ar_3$   
groups, said additional  $-Ar_3$  groups are not substituted  
with another  $-Ar_3$ .

The ICE inhibitors of another embodiment (C) of this invention are those of formula (II):

20



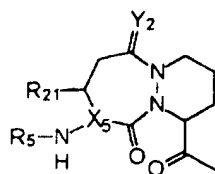
wherein:

$m$  is 1 or 2;

$R_1$  is selected from the group consisting of the following formulae:

25

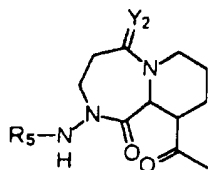
(e10)



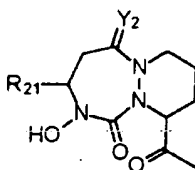


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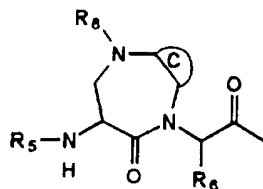
(e11)



(e12)

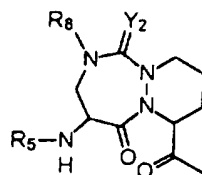


(w2)

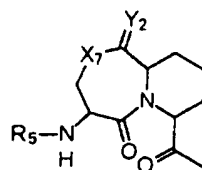


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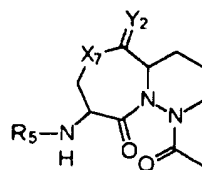
(y1)



(y2)



(z)



; and

10

ring C is chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

- 52 -

$R_3$  is selected from the group consisting of:

- CN,
- C(O)-H,
- C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>,
- 5 -C(O)-CH<sub>2</sub>-F,
- C=N-O-R<sub>9</sub>, and
- CO-Ar<sub>2</sub>;

$R_5$  is selected from the group consisting of:

- C(O)-R<sub>10</sub>,
- 10 -C(O)O-R<sub>9</sub>,
- $$\begin{array}{c} R_{10} \\ / \\ -C(O)-N \\ \backslash \\ R_{10} \end{array}$$
- 15 -S(O)<sub>2</sub>-R<sub>9</sub>,
- C(O)-CH<sub>2</sub>-O-R<sub>9</sub>,
- C(O)C(O)-R<sub>10</sub>,
- 20 -R<sub>9</sub>,
- H, and
- C(O)C(O)-OR<sub>10</sub>,

$X_5$  is  $\begin{array}{c} -CH- \\ | \end{array}$  or  $\begin{array}{c} -N- \\ | \end{array}$ ;

25  $Y_2$  is H<sub>2</sub> or O;

$X_7$  is -N(R<sub>8</sub>)- or -O-;

each T<sub>1</sub> is independently selected from the group consisting of -O-, -S-, -S(O)-, and -S(O)<sub>2</sub>-;

30

$R_6$  is selected from the group consisting of -H and -CH<sub>3</sub>;

$R_8$  is selected from the group consisting of:

- 53 -

5  
10  
15  
20  
25  
30

-C(O)-R<sub>10</sub>,  
-C(O)O-R<sub>9</sub>,  
-C(O)-NH-R<sub>10</sub>,  
-S(O)<sub>2</sub>-R<sub>9</sub>,  
-S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
-C(O)-CH<sub>2</sub>-OR<sub>10</sub>,  
-C(O)C(O)-R<sub>10</sub>,  
-C(O)-CH<sub>2</sub>-N(R<sub>10</sub>)(R<sub>10</sub>),  
-C(O)-CH<sub>2</sub>C(O)-O-R<sub>9</sub>,  
-C(O)-CH<sub>2</sub>C(O)-R<sub>9</sub>,  
-H, and  
-C(O)-C(O)-OR<sub>10</sub>;

each R<sub>9</sub> is independently selected from the group consisting of -Ar<sub>3</sub> and a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, wherein the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

each R<sub>10</sub> is independently selected from the group consisting of -H, -Ar<sub>3</sub>, a C<sub>3-6</sub> cycloalkyl group, and a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, wherein the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

each R<sub>11</sub> is independently selected from the group consisting of:

25  
30

-Ar<sub>4</sub>,  
-(CH<sub>2</sub>)<sub>1-3</sub>-Ar<sub>4</sub>,  
-H, and  
-C(O)-Ar<sub>4</sub>;

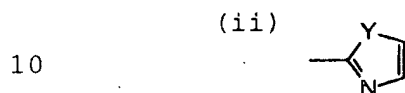
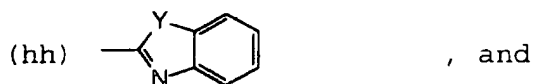
R<sub>13</sub> is selected from the group consisting of H, Ar<sub>3</sub>, and a C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, -CONH<sub>2</sub>, -OR<sub>5</sub>, -OH, -OR<sub>9</sub>, or -CO<sub>2</sub>H;

- 54 -

-OR<sub>13</sub> is optionally -N(H)-OH;

each R<sub>21</sub> is independently selected from the group consisting of -H or a -C<sub>1-6</sub> straight or branched alkyl group;

5 Ar<sub>2</sub> is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by -Q<sub>1</sub>:



wherein each Y is independently selected from the group consisting of O and S;

each Ar<sub>3</sub> is a cyclic group independently selected from the set consisting of an aryl group which contains  
15 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, and -NH-,  
20 -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

25 each Ar<sub>4</sub> is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and

- 55 -

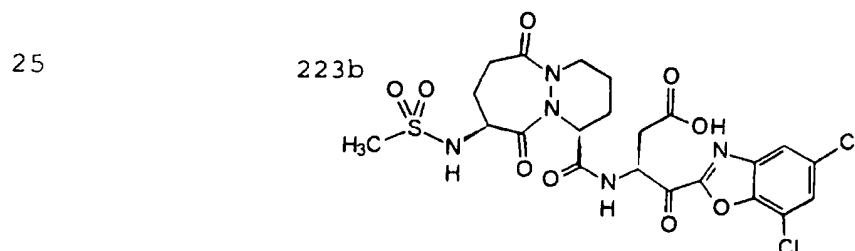
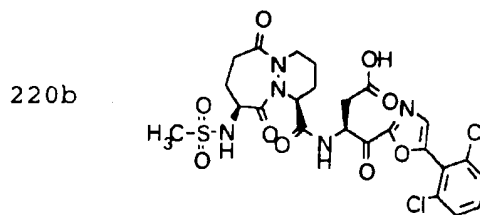
15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, -NH-, -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally  
 5 containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

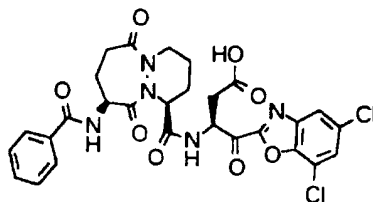
each Q<sub>1</sub> is independently selected from the group  
 10 consisting of -NH<sub>2</sub>, -CO<sub>2</sub>H, -Cl, -F, -Br, -I, -NO<sub>2</sub>, -CN, =O, -OH, -perfluoro C<sub>1-3</sub> alkyl, R<sub>5</sub>, -OR<sub>5</sub>, -NHR<sub>5</sub>, OR<sub>9</sub>, -NHR<sub>9</sub>, R<sub>9</sub>, -C(O)-R<sub>10</sub>, and



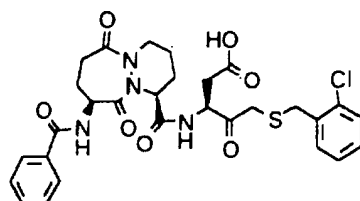
provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub>  
 20 group which comprises one or more additional -Ar<sub>3</sub> with another -Ar<sub>3</sub>.

Preferred compounds of this embodiment include, but are not limited to:

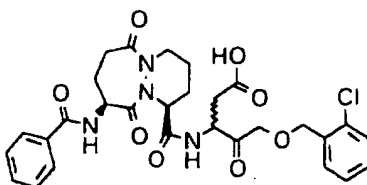




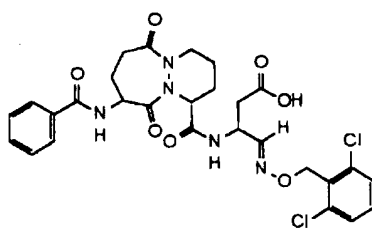
226e



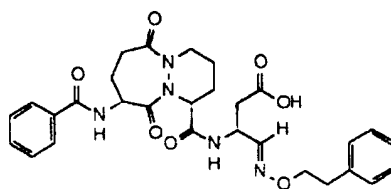
227e



307a

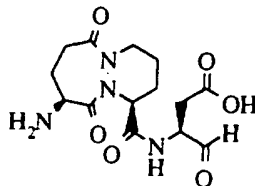


307b

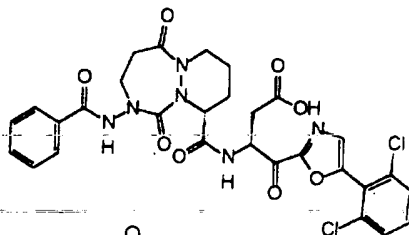


- 57 -

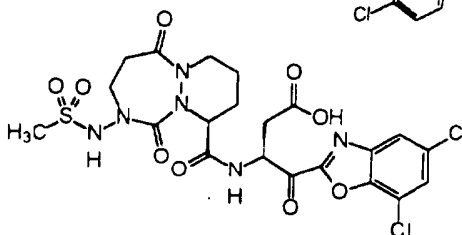
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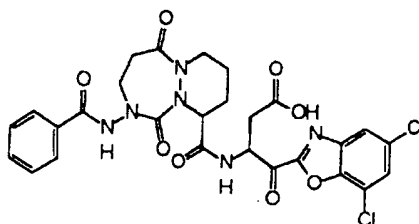
820b



823b

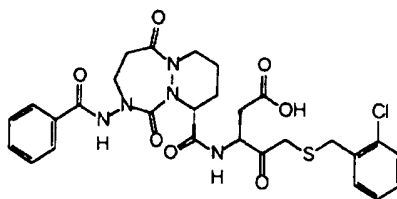


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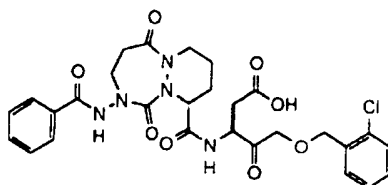


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826e

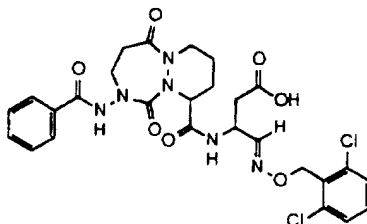


827e

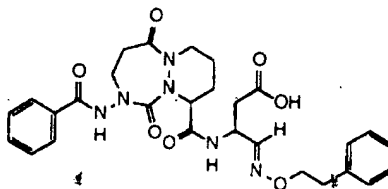


- 58 -

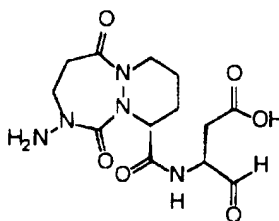
907a



907b



1029



Preferred compounds of embodiment C employ  
 5 formula (II), wherein  $R_1$  is (e11) and the other  
 substituents are as defined above.

Other preferred compounds of embodiment C  
 employ formula (II), wherein  $R_1$  is (e12) and the other  
 substituents are as defined above.

10 Other preferred compounds of embodiment C  
 employ formula (II) wherein  $R_1$  is (y1) and the other  
 substituents are as defined above.

Other preferred compounds of embodiment C  
 15 employ formula (II) wherein  $R_1$  is (y2) and the other  
 substituents are as defined above.



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Other preferred compounds of embodiment C of employ formula (II) wherein  $R_1$  is (z) and the other substituents are as defined above.

5 Other preferred compound of embodiment C employ formula (II) wherein  $R_1$  is (w2) and the other substituents are as defined above.

More preferably,  $R_1$  is (w2) and

m is 1;

ring C is benzo, pyrido, or thieno;

10  $R_3$  is selected from the group consisting of -C(O)-H, -C(O)-Ar<sub>2</sub>, and -C(O)CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>;

$R_5$  is selected from the group consisting of:

-C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is -Ar<sub>3</sub>;

-C(O)O-R<sub>9</sub>, wherein R<sub>9</sub> is -CH<sub>2</sub>-Ar<sub>3</sub>;

15 -C(O)C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is -CH<sub>2</sub>Ar<sub>3</sub>;

-R<sub>9</sub>, wherein R<sub>9</sub> is a C<sub>1-2</sub> alkyl group substituted with -Ar<sub>3</sub>; and

-C(O)C(O)-OR<sub>10</sub>, wherein R<sub>10</sub> is -CH<sub>2</sub>Ar<sub>3</sub>;

20 T<sub>1</sub> is O or S;

R<sub>6</sub> is H;

R<sub>8</sub> is selected from the group consisting -C(O)-R<sub>10</sub>, -C(O)-CH<sub>2</sub>-OR<sub>10</sub>, and -C(O)CH<sub>2</sub>-N(R<sub>10</sub>)(R<sub>10</sub>), wherein R<sub>10</sub> is H, CH<sub>3</sub>, or -CH<sub>2</sub>CH<sub>3</sub>;

25 R<sub>11</sub> is selected from the group consisting of -Ar<sub>4</sub>, -(CH<sub>2</sub>)<sub>1-3</sub>-Ar<sub>4</sub>, and -C(O)-Ar<sub>4</sub>;

- 60 -

R<sub>13</sub> is H or a -C<sub>1-4</sub> straight or branched alkyl group optionally substituted with -Ar<sub>3</sub>, -OH, -OR<sub>9</sub>, or -CO<sub>2</sub>H, wherein the R<sub>9</sub> is a -C<sub>1-4</sub> branched or straight alkyl group, wherein Ar<sub>3</sub> is morpholinyl or phenyl,  
 5 wherein the phenyl is optionally substituted with Q<sub>1</sub>;

Ar<sub>2</sub> is (hh);

Y is O;

Ar<sub>3</sub> is phenyl, naphthyl, thienyl, quinolinyl,  
 10 isoquinolinyl, thiazolyl, benzimidazolyl, thienothienyl, thiadiazolyl, benzotriazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl;

Ar<sub>4</sub> is phenyl, tetrazolyl, naphthyl, pyridinyl, oxazolyl, pyrimidinyl, or indolyl;

15 each Q<sub>1</sub> is independently selected from the group consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -NHR<sub>9</sub>, and



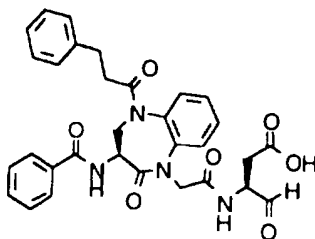
wherein each R<sub>9</sub> and R<sub>10</sub> are independently a -C<sub>1-6</sub>  
 25 straight or branched alkyl group optionally substituted with Ar<sub>3</sub> wherein Ar<sub>3</sub> is phenyl;

provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub> group which comprises one or more additional -Ar<sub>3</sub>  
 30 groups, said additional -Ar<sub>3</sub> groups are not substituted with another -Ar<sub>3</sub>.

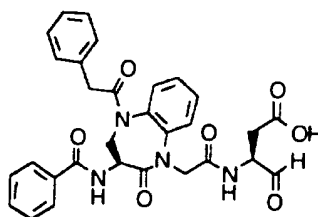
- 61 -

Preferred compounds of this embodiment include, but are not limited to:

605a

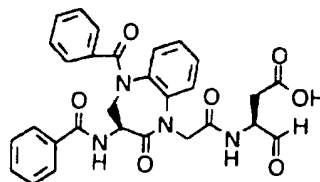


605b

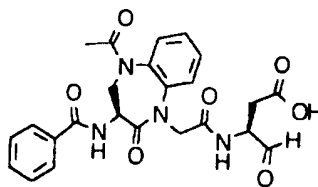


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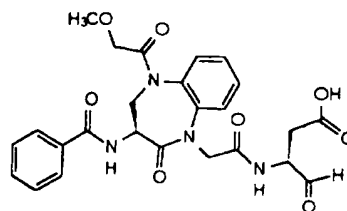
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605d

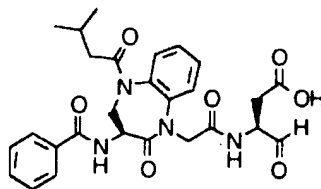


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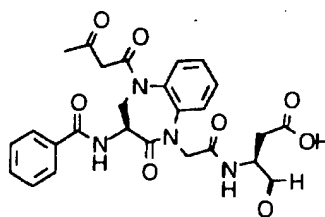


- 62 -

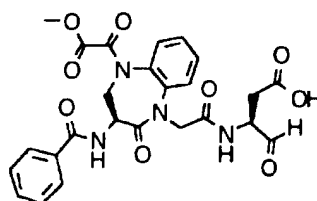
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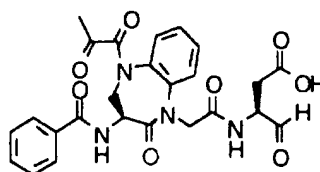
605g



605h

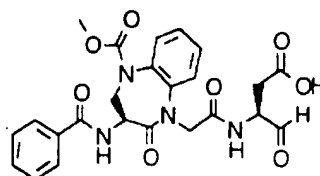


605i

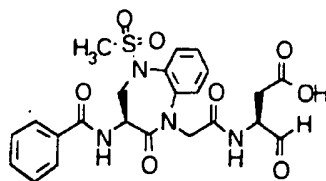


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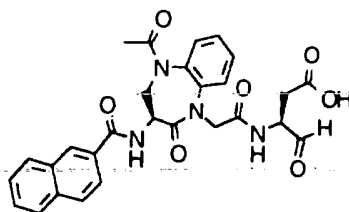
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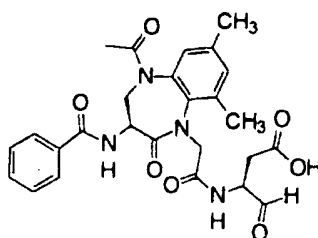
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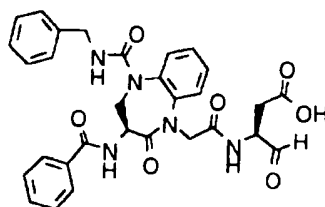
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6050

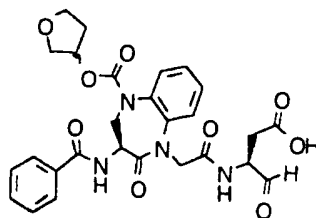


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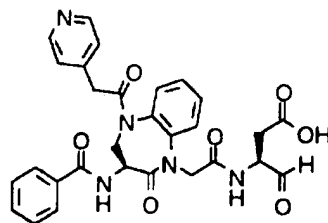
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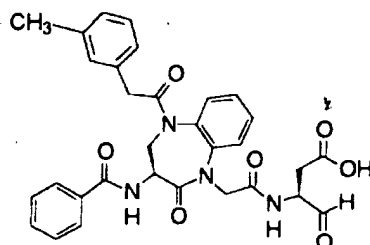


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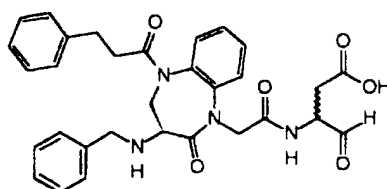
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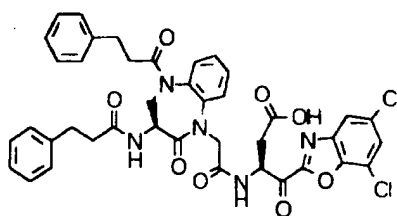
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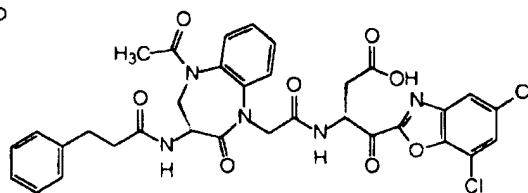


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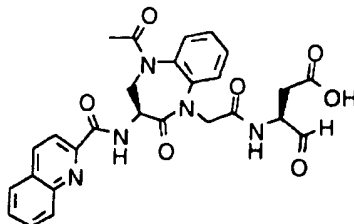
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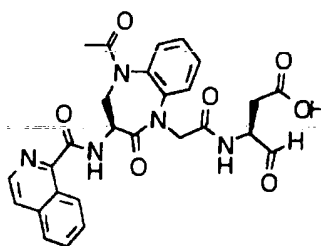


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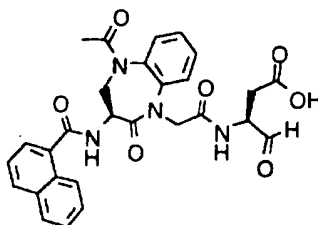
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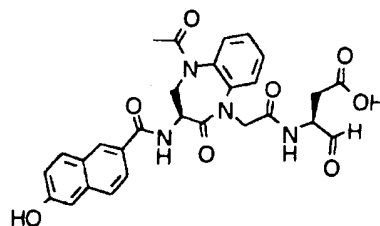
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621

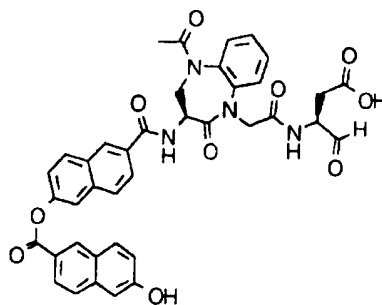


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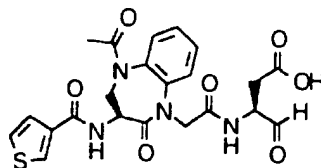
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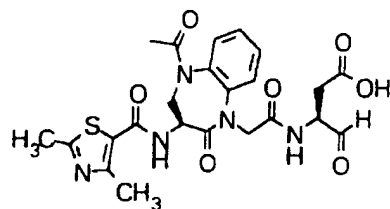


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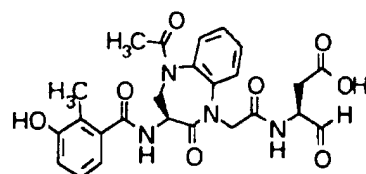
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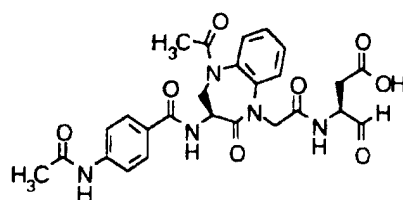
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626

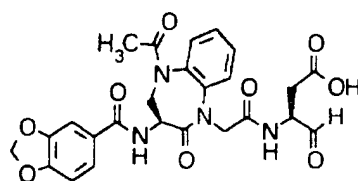


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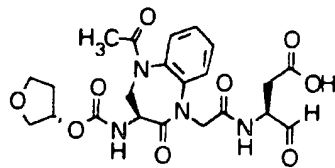
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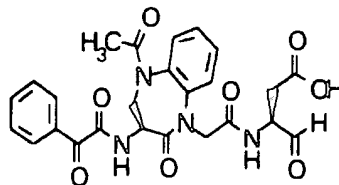


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635



Other preferred compounds of embodiment C  
employ formula (II) wherein  $R_1$  is (e10),  $X_5$  is CH, and  
5 the other substituents are as defined above.

More preferred compounds of embodiment C  
employ formula (II) wherein  $R_1$  is (e10),  $X_5$  is CH,  $R_3$  is  
CO-Ar<sub>2</sub>, and the other substituents are as defined  
above.

10 Other more preferred compounds of embodiment  
C employ formula (II) wherein  $R_1$  is (e10),  $X_5$  is CH,  $R_3$   
is -C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>,  $R_{11}$  is -(CH<sub>2</sub>)<sub>1-3</sub>-Ar<sub>4</sub>, and the other  
substituents are as defined above.

Other more preferred compounds of embodiment  
15 C employ formula (II) wherein  $R_1$  is (e10) and  $X_5$  is CH  
and

$R_3$  is -C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>;

T<sub>1</sub> is O; and

$R_{11}$  is -C(O)-Ar<sub>4</sub>,

20 and the other substituents are as defined above.

More preferably, in these more preferred compounds,  $R_5$   
is selected from the group consisting of:

-C(O)-R<sub>10</sub>,

-C(O)O-R<sub>9</sub>, and

25 -C(O)-NH-R<sub>10</sub>.

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Alternatively, in these more preferred compounds,  $R_5$  is selected from the group consisting of:

- 5            $-S(O)_2-R_9$ ,  
             $-S(O)_2-NH-R_{10}$ ,  
             $-C(O)-C(O)-R_{10}$ ,  
             $-R_9$ , and  
             $-C(O)-C(O)-OR_{10}$ .

Most preferably, in these more preferred compounds,

10            $m$  is 1;

$T_1$  is O or S;

15            $R_{13}$  is H or a  $-C_{1-4}$  straight or branched alkyl group optionally substituted with  $-Ar_3$ ,  $-OH$ ,  $-OR_9$ , or  $-CO_2H$ , wherein the  $R_9$  is a  $-C_{1-4}$  branched or straight alkyl group, wherein  $Ar_3$  is morpholinyl or phenyl, wherein the phenyl is optionally substituted with  $Q_1$ ;

$R_{21}$  is  $-H$  or  $-CH_3$ ;

20            $R_{51}$  is a  $C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$ , wherein  $Ar_3$  is phenyl, optionally substituted by  $-Q_1$ ;

$Ar_2$  is (hh);

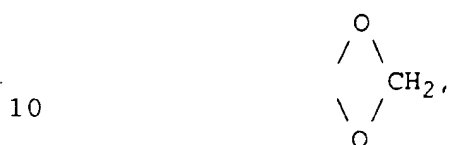
$Y$  is O, and

25            $Ar_3$  is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl benzofuranyl, and indolyl;

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Ar<sub>4</sub> is phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl;

each Q<sub>1</sub> is independently selected from the group consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -NHR<sub>9</sub>, and



wherein each R<sub>9</sub> and R<sub>10</sub> are independently a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub> wherein Ar<sub>3</sub> is phenyl;

15

provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub> group which comprises one or more additional -Ar<sub>3</sub> groups, said additional -Ar<sub>3</sub> groups are not substituted with another -Ar<sub>3</sub>.

20

Other more preferred compounds of embodiment C employ formula (II) wherein R<sub>1</sub> is (e10), X<sub>5</sub> is CH, R<sub>3</sub> is -C(O)-H, and the other substituents are as defined above.

More preferably, in these more preferred compounds, R<sub>5</sub> is selected from the group consisting of:

25

-C(O)-R<sub>10</sub>,  
-C(O)O-R<sub>9</sub>, and  
-C(O)-NH-R<sub>10</sub>.

Alternatively, in these more preferred compounds, R<sub>5</sub> is selected from the group consisting of:

30

-S(O)<sub>2</sub>-R<sub>9</sub>,  
-S(O)<sub>2</sub>-NH-R<sub>10</sub>,

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-C(O)-C(O)-R<sub>10</sub>,  
-R<sub>9</sub>, and  
-C(O)-C(O)-OR<sub>10</sub>.

Most preferably, in these more preferred compounds,

5           m is 1;

T<sub>1</sub> is O or S;

10           R<sub>13</sub> is H or a -C<sub>1-4</sub> straight or branched alkyl  
group optionally substituted with -Ar<sub>3</sub>, -OH, -OR<sub>9</sub>, or  
-CO<sub>2</sub>H, wherein the R<sub>9</sub> is a -C<sub>1-4</sub> branched or straight  
alkyl group, wherein Ar<sub>3</sub> is morpholinyl or phenyl,  
wherein the phenyl is optionally substituted with Q<sub>1</sub>;

R<sub>21</sub> is -H or -CH<sub>3</sub>;

15           R<sub>51</sub> is a C<sub>1-6</sub> straight or branched alkyl group  
optionally substituted with Ar<sub>3</sub>, wherein Ar<sub>3</sub> is phenyl,  
optionally substituted by -Q<sub>1</sub>;

Ar<sub>2</sub> is (hh);

Y is O, and

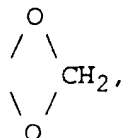
20           Ar<sub>3</sub> is phenyl, naphthyl, thienyl, quinolinyl,  
isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl,  
benzotriazolyl, benzimidazolyl, thienothienyl,  
imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl  
benzofuranyl, and indolyl;

25           Ar<sub>4</sub> is phenyl, tetrazolyl, pyridinyl, oxazolyl,  
naphthyl, pyrimidinyl, or thienyl;

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each  $Q_1$  is independently selected from the group consisting of  $-NH_2$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-OH$ ,  $-R_9$ ,  $-NH-R_5$  wherein  $R_5$  is  $-C(O)-R_{10}$  or  $-S(O)_2-R_9$ ,  $-OR_5$  wherein  $R_5$  is  $-C(O)-R_{10}$ ,  $-OR_9$ ,  $-NHR_9$ , and

5



10 wherein each  $R_9$  and  $R_{10}$  are independently a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$  wherein  $Ar_3$  is phenyl;

15 provided that when  $-Ar_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-Ar_3$  groups, said additional  $-Ar_3$  groups are not substituted with another  $-Ar_3$ ,

Other more preferred compounds of embodiment C employ formula (II) wherein  $R_1$  is (e10) and  $X_5$  is  $CH$ ,  
 20  $R_3$  is  $-CO-CH_2-T_1-R_{11}$ , and  $R_{11}$  is  $-Ar_4$ , and the other substituents are as defined above.

More preferably, in these more preferred compounds,  $R_5$  is selected from the group consisting of:

25  $-C(O)-R_{10}$ ,  
 $-C(O)O-R_9$ , and  
 $-C(O)-NH-R_{10}$ .

Alternatively, in these more preferred compounds,  $R_5$  is selected from the group consisting of:

$-S(O)_2-R_9$ ,

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-S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
-C(O)-C(O)-R<sub>10</sub>,  
-R<sub>9</sub>, and  
-C(O)-C(O)-OR<sub>10</sub>.

5 Most preferably, in these more preferred compounds,

m is 1;

T<sub>1</sub> is O or S;

10 R<sub>13</sub> is H or a -C<sub>1-4</sub> straight or branched alkyl group optionally substituted with -Ar<sub>3</sub>, -OH, -OR<sub>9</sub>, or -CO<sub>2</sub>H, wherein the R<sub>9</sub> is a -C<sub>1-4</sub> branched or straight alkyl group, wherein Ar<sub>3</sub> is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q<sub>1</sub>;

R<sub>21</sub> is -H or -CH<sub>3</sub>;

15 R<sub>51</sub> is a C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, wherein Ar<sub>3</sub> is phenyl, optionally substituted by -Q<sub>1</sub>;

Ar<sub>2</sub> is (hh);

Y is O, and

20

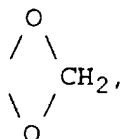
Ar<sub>3</sub> is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl  
25 benzofuranyl, and indolyl;

Ar<sub>4</sub> is phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl;

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each  $Q_1$  is independently selected from the group consisting of  $-NH_2$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-OH$ ,  $-R_9$ ,  $-NH-R_5$  wherein  $R_5$  is  $-C(O)-R_{10}$  or  $-S(O)_2-R_9$ ,  $-OR_5$  wherein  $R_5$  is  $-C(O)-R_{10}$ ,  $-OR_9$ ,  $-NHR_9$ , and

5



10 wherein each  $R_9$  and  $R_{10}$  are independently a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$  wherein  $Ar_3$  is phenyl;

15 provided that when  $-Ar_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-Ar_3$  groups, said additional  $-Ar_3$  groups are not substituted with another  $-Ar_3$ .

Other preferred compounds of embodiment C employ formula (II) wherein  $R_1$  is (e10),  $X_5$  is N, and  
20 the other substituents are as defined above.

More preferred compounds of embodiment C, employ formula (II) wherein  $R_1$  is (e10),  $X_5$  is N,  $R_3$  is  $CO-Ar_2$ , and the other substituents are as defined above.

25 Other more preferred compounds of embodiment C, employ formula (II) wherein  $R_1$  is (e10),  $X_5$  is N,  $R_3$  is  $-C(O)-CH_2-T_1-R_{11}$ ,  $R_{11}$  is  $-(CH_2)_{1-3}-Ar_4$ , and the other substituents are as defined above.

30 Other more preferred compounds of embodiment C, employ formula (II) wherein  $R_1$  is (e10) and  $X_5$  is N and:



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$R_3$  is  $-C(O)-CH_2-T_1-R_{11}$ ;

$T_1$  is O; and

$R_{11}$  is  $-C(O)-Ar_4$ , and the other substituents are as defined above.

5 More preferably, in these more preferred compounds,  $R_5$  is selected from the group consisting of:

$-C(O)-R_{10}$ ,

$-C(O)O-R_9$ , and

$-C(O)-NH-R_{10}$ .

10 Alternatively, in these more preferred compounds,  $R_5$  is selected from the group consisting of:

$-S(O)_2-R_9$ ,

$-S(O)_2-NH-R_{10}$ ,

$-C(O)-C(O)-R_{10}$ ,

15  $-R_9$ , and

$-C(O)-C(O)-OR_{10}$ .

Most preferably, in these more preferred compounds,  $R_5$  is selected from the group consisting of:

$-S(O)_2-R_9$ ,

20  $-S(O)_2-NH-R_{10}$ ,

$-C(O)-C(O)-R_{10}$ ,

$-R_9$ , and

$-C(O)-C(O)-OR_{10}$ .

$m$  is 1;

25

$T_1$  is O or S;

$R_{13}$  is H or a  $-C_{1-4}$  straight or branched alkyl group optionally substituted with  $-Ar_3$ ,  $-OH$ ,  $-OR_9$ , or  $-CO_2H$ , wherein the  $R_9$  is a  $-C_{1-4}$  branched or straight alkyl group, wherein  $Ar_3$  is morpholinyl or phenyl, wherein the phenyl is optionally substituted with  $Q_1$ ;

30

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$R_{21}$  is -H or -CH<sub>3</sub>;

$R_{51}$  is a C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, wherein Ar<sub>3</sub> is phenyl, optionally substituted by -Q<sub>1</sub>;

5           Ar<sub>2</sub> is (hh);

Y is O, and

10           Ar<sub>3</sub> is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl benzofuranyl, and indolyl;

Ar<sub>4</sub> is phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl;

15           each Q<sub>1</sub> is independently selected from the group consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -NHR<sub>9</sub>, and



25           wherein each R<sub>9</sub> and R<sub>10</sub> are independently a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub> wherein Ar<sub>3</sub> is phenyl;

30           provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub> group which comprises one or more additional -Ar<sub>3</sub> groups, said additional -Ar<sub>3</sub> groups are not substituted with another -Ar<sub>3</sub>.

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Other more preferred compounds of embodiment C, employ formula (II) wherein  $R_1$  is (e10),  $X_5$  is N,  $R_3$  is  $-C(O)-H$ , and the other substituents are as defined above.

5 More preferably, in these more preferred compounds,  $R_5$  is selected from the group consisting of:

$-C(O)-R_{10}$ ,  
 $-C(O)O-R_9$ , and  
 $-C(O)-NH-R_{10}$ .

10 Alternatively, in these more preferred compounds,  $R_5$  is selected from the group consisting of:

$-S(O)_2-R_9$ ,  
 $-S(O)_2-NH-R_{10}$ ,  
 $-C(O)-C(O)-R_{10}$ ,  
15  $-R_9$ , and  
 $-C(O)-C(O)-OR_{10}$ .

Most preferably, in these more preferred compounds,

$m$  is 1;

20  $T_1$  is O or S;

$R_{13}$  is H or a  $-C_{1-4}$  straight or branched alkyl group optionally substituted with  $-Ar_3$ ,  $-OH$ ,  $-OR_9$ , or  $-CO_2H$ , wherein the  $R_9$  is a  $-C_{1-4}$  branched or straight alkyl group, wherein  $Ar_3$  is morpholinyl or phenyl,  
25 wherein the phenyl is optionally substituted with  $Q_1$ ;

$R_{21}$  is  $-H$  or  $-CH_3$ ;

$R_{51}$  is a  $C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$ , wherein  $Ar_3$  is phenyl, optionally substituted by  $-Q_1$ ;

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Ar<sub>2</sub> is (hh);

Y is O, and

Ar<sub>3</sub> is phenyl, naphthyl, thienyl, quinolinyl,  
 5 isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl,  
 benzotriazolyl, benzimidazolyl, thienothienyl,  
 imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl  
 benzofuranyl, and indolyl;

Ar<sub>4</sub> is phenyl, tetrazolyl, pyridinyl, oxazolyl,  
 10 naphthyl, pyrimidinyl, or thienyl;

each Q<sub>1</sub> is independently selected from the group  
 consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub>  
 wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is  
 -C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -NHR<sub>9</sub>, and



20 wherein each R<sub>9</sub> and R<sub>10</sub> are independently a -C<sub>1-6</sub>  
 straight or branched alkyl group optionally substituted  
 with Ar<sub>3</sub> wherein Ar<sub>3</sub> is phenyl;

provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub>  
 25 group which comprises one or more additional -Ar<sub>3</sub>  
 groups, said additional -Ar<sub>3</sub> groups are not substituted  
 with another -Ar<sub>3</sub>.

Other more preferred compounds of embodiment  
 C, employ formula (II) wherein R<sub>1</sub> is (e10), X<sub>5</sub> is N, R<sub>3</sub>  
 30 is -CO-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>, R<sub>11</sub> is -Ar<sub>4</sub>, and the other  
 substituents are as defined above.

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More preferably, in these more preferred compounds,  $R_5$  is selected from the group consisting of:

- C(O)- $R_{10}$ ,
- C(O)O- $R_9$ , and
- 5        -C(O)-NH- $R_{10}$ .

Alternatively, in these more preferred compounds,  $R_5$  is selected from the group consisting of:

- S(O)<sub>2</sub>- $R_9$ ,
- S(O)<sub>2</sub>-NH- $R_{10}$ ,
- 10       -C(O)-C(O)- $R_{10}$ ,
- $R_9$ , and
- C(O)-C(O)-OR<sub>10</sub>.

Most preferably, in these more preferred compounds

15         $m$  is 1;

$T_1$  is O or S;

20         $R_{13}$  is H or a -C<sub>1-4</sub> straight or branched alkyl group optionally substituted with -Ar<sub>3</sub>, -OH, -OR<sub>9</sub>, or -CO<sub>2</sub>H, wherein the  $R_9$  is a -C<sub>1-4</sub> branched or straight alkyl group, wherein Ar<sub>3</sub> is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q<sub>1</sub>;

$R_{21}$  is -H or -CH<sub>3</sub>;

25         $R_{51}$  is a C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, wherein Ar<sub>3</sub> is phenyl, optionally substituted by -Q<sub>1</sub>;

Ar<sub>2</sub> is (hh);

Y is O, and

- 80 -

Ar<sub>3</sub> is phenyl, naphthyl, thienyl, quinolinyl,  
 isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl,  
 benzotriazolyl, benzimidazolyl, thienothienyl,  
 imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl  
 5 benzofuranyl, and indolyl;

Ar<sub>4</sub> is phenyl, tetrazolyl, pyridinyl, oxazolyl,  
 naphthyl, pyrimidinyl, or thienyl;

each Q<sub>1</sub> is independently selected from the group  
 consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub>  
 10 wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is  
 -C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -NHR<sub>9</sub>, and



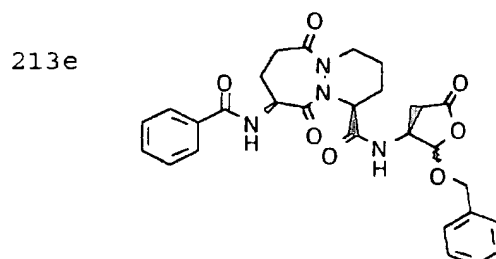
wherein each R<sub>9</sub> and R<sub>10</sub> are independently a -C<sub>1-6</sub>  
 straight or branched alkyl group optionally substituted  
 with Ar<sub>3</sub> wherein Ar<sub>3</sub> is phenyl;

20

provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub>  
 group which comprises one or more additional -Ar<sub>3</sub>  
 groups, said additional -Ar<sub>3</sub> groups are not substituted  
 with another -Ar<sub>3</sub>.

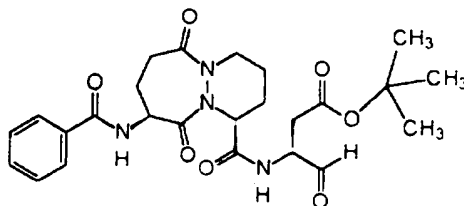
25

Preferred compounds of embodiment B include,  
 but are not limited to:

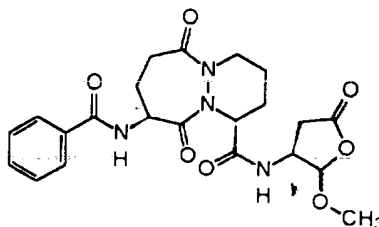


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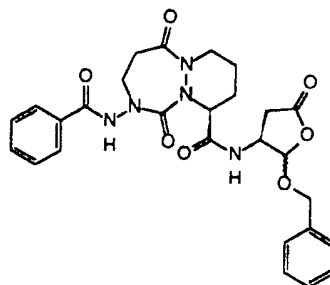
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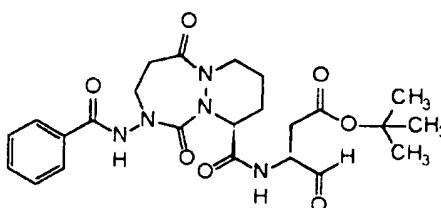
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813e

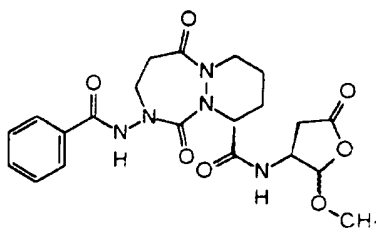


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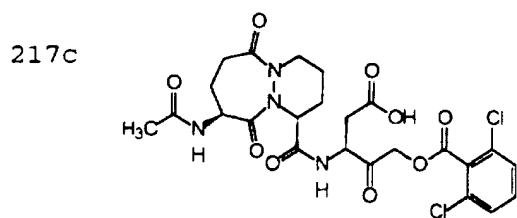
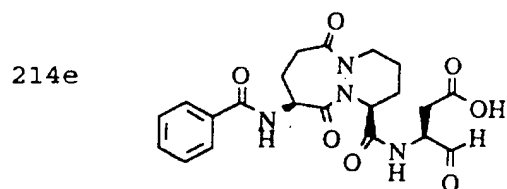
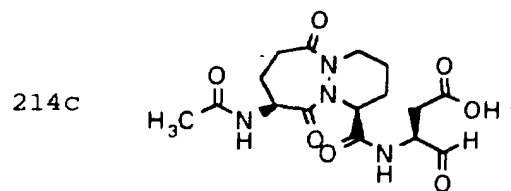
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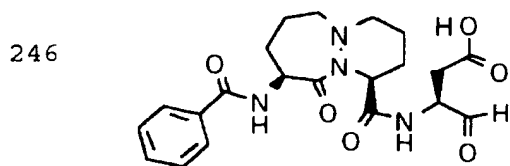
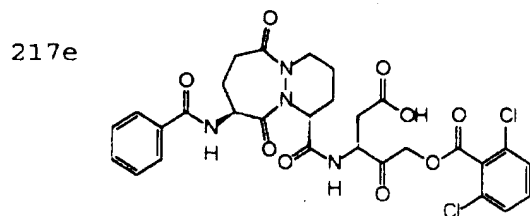
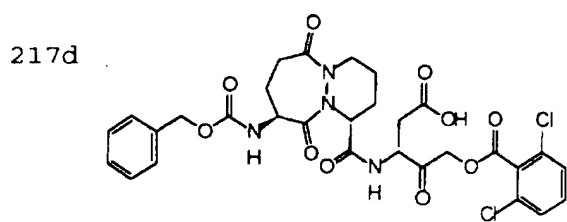


Preferred compounds of embodiment C include,  
but are not limited to:

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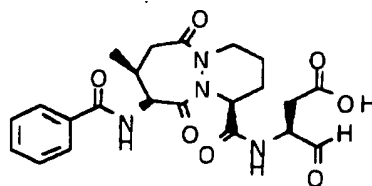
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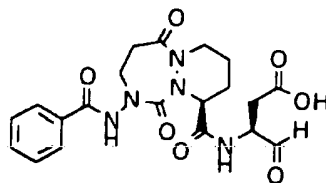


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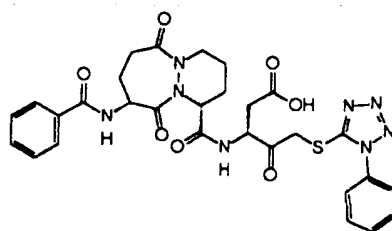
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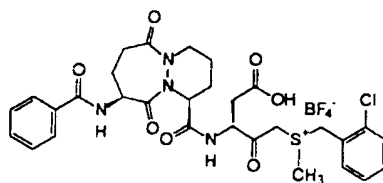
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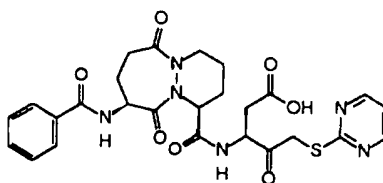


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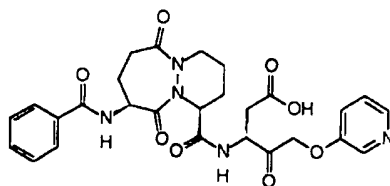


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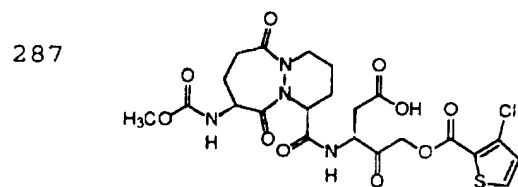
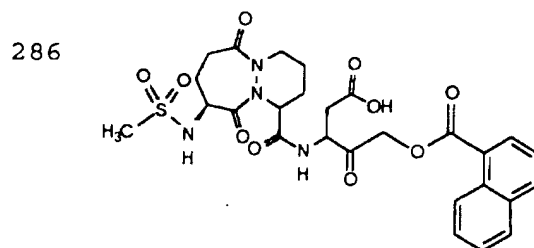
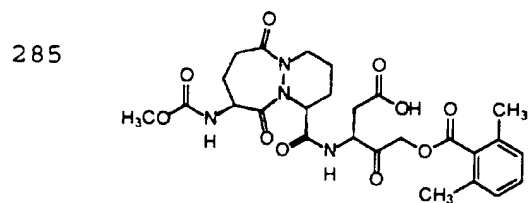
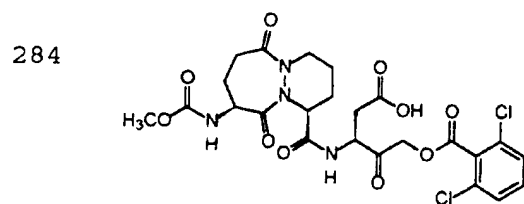
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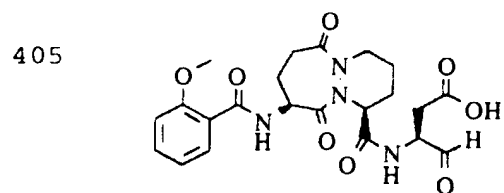
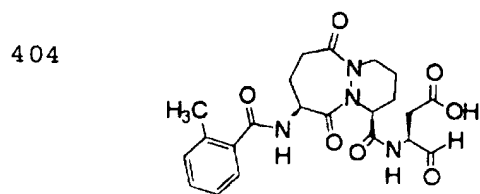
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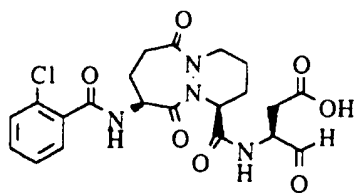
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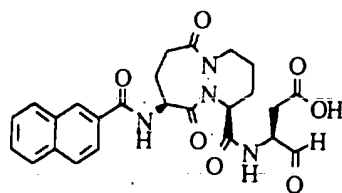
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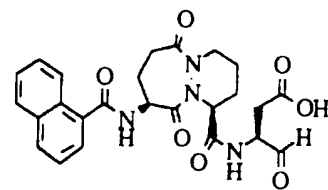
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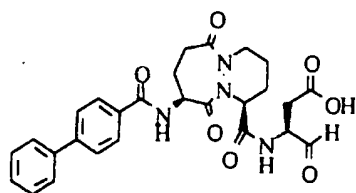
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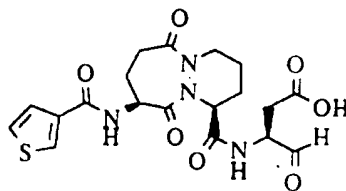


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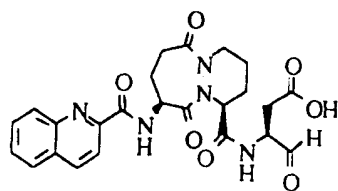


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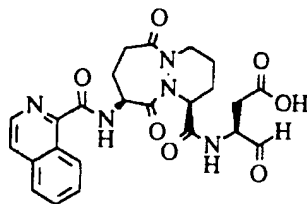


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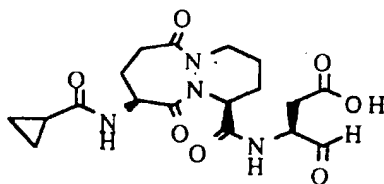


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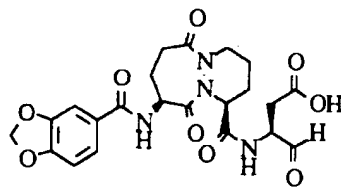
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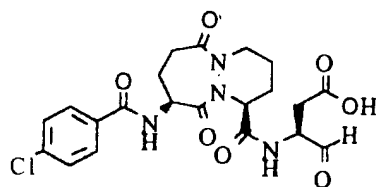
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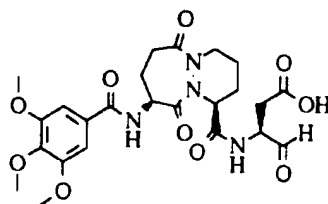


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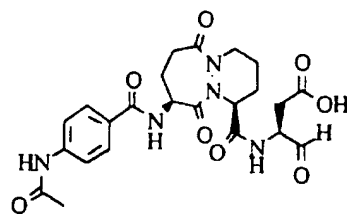


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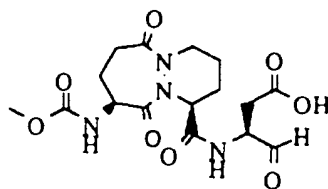


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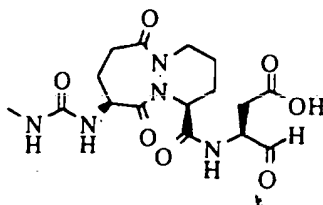


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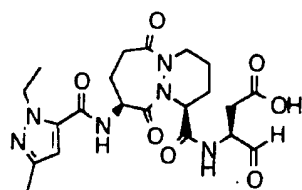
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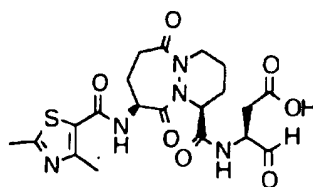
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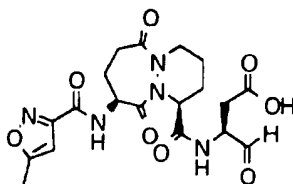


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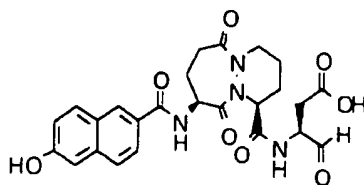


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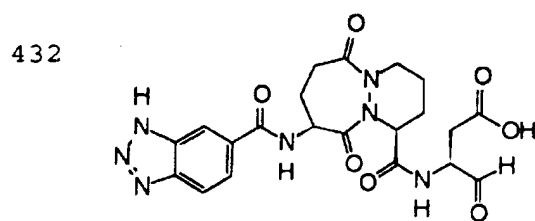
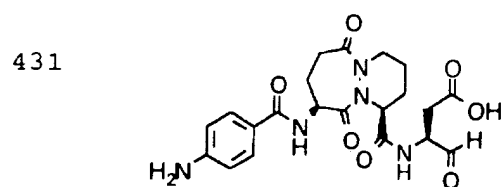
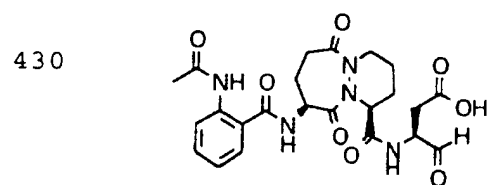
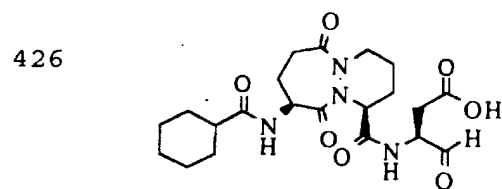
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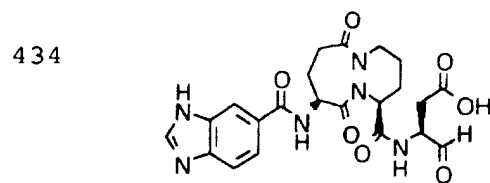
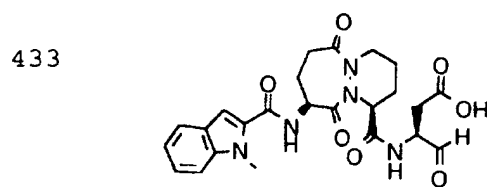
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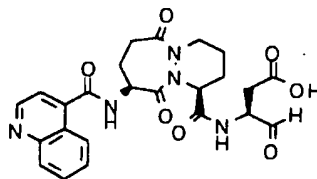


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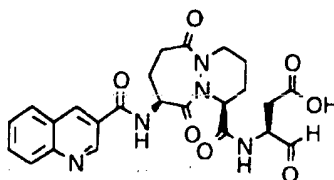


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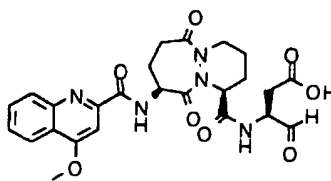
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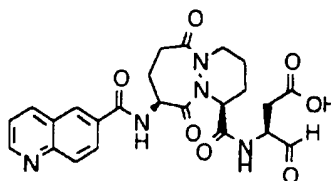
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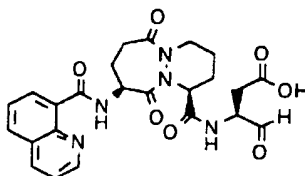


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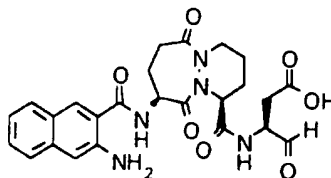


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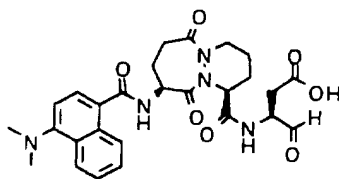
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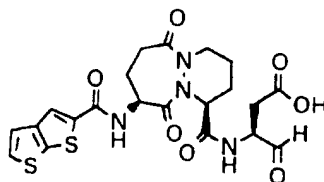
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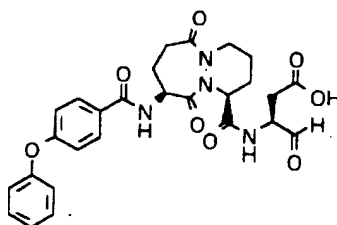
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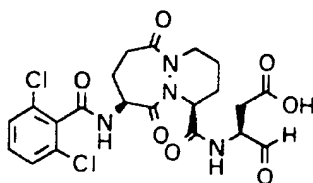
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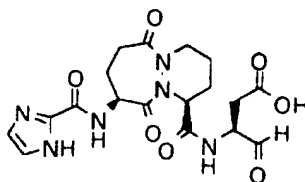
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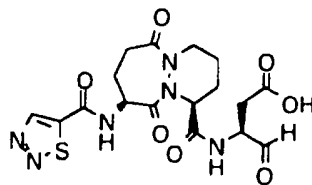
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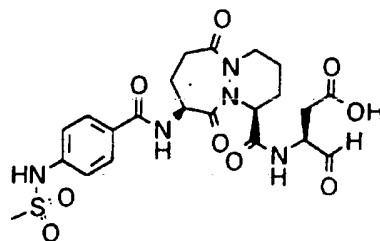


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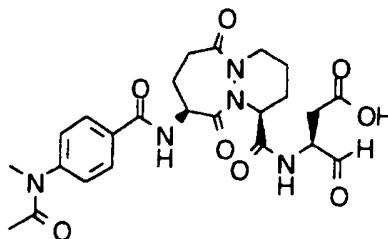
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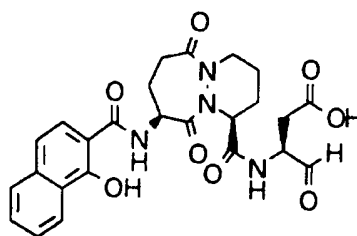
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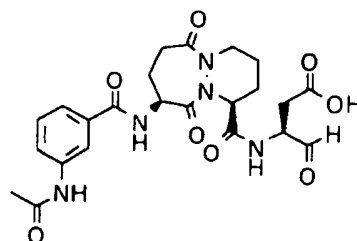


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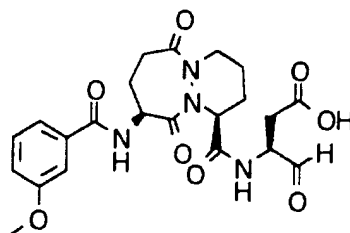
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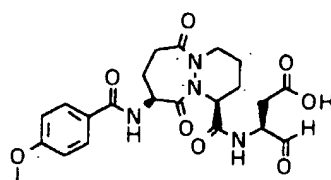


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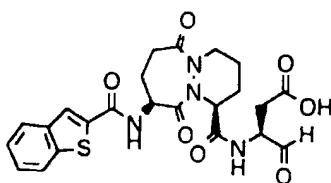
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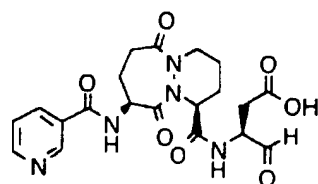
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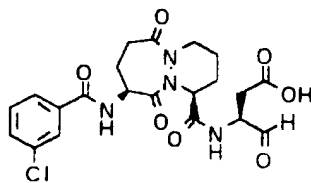


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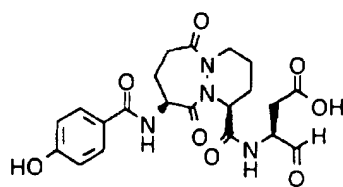


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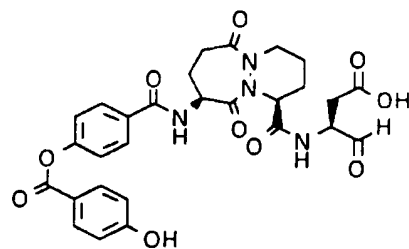


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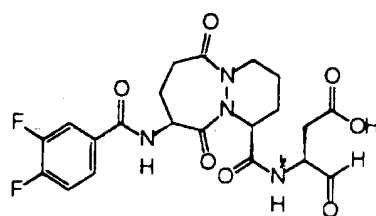


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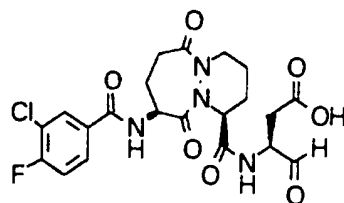
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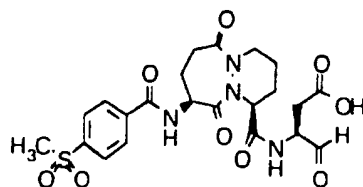
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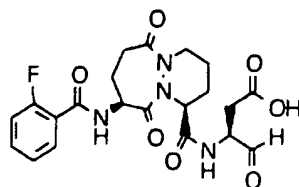


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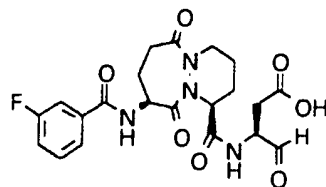


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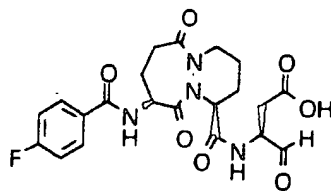


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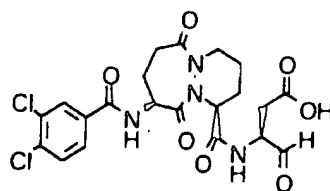


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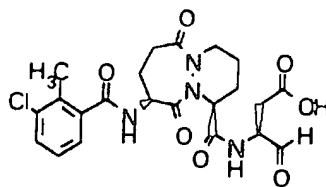
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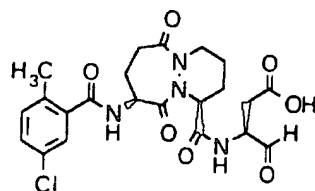
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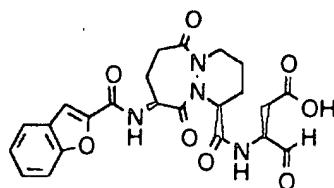


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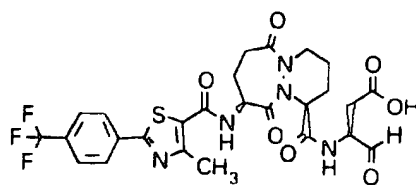


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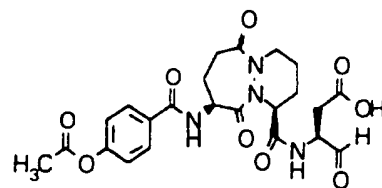
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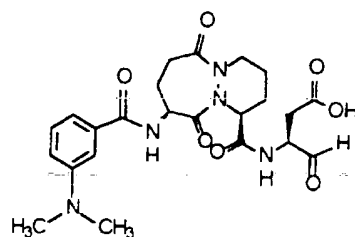
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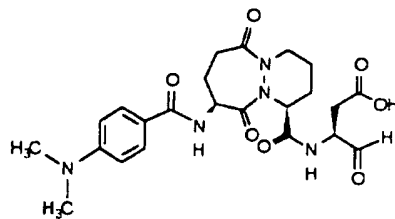
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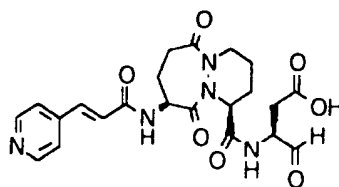
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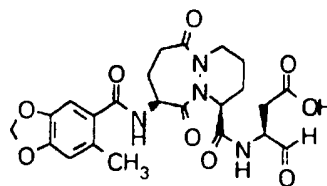


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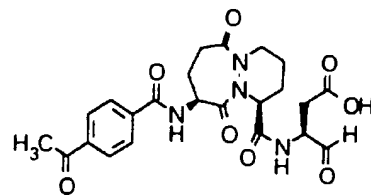
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473

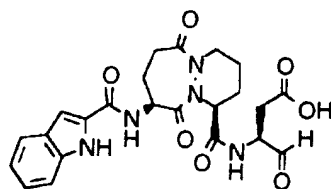


- 96 -

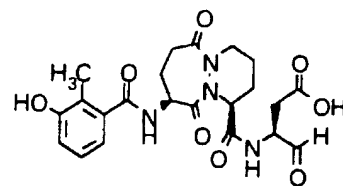
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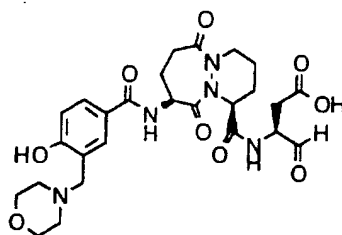
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476

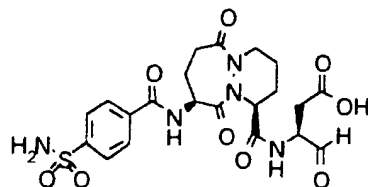


477



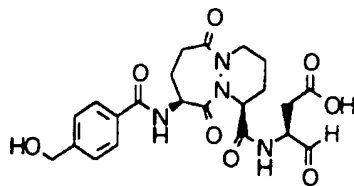
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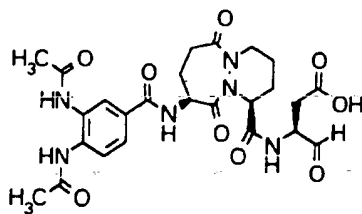


- 97 -

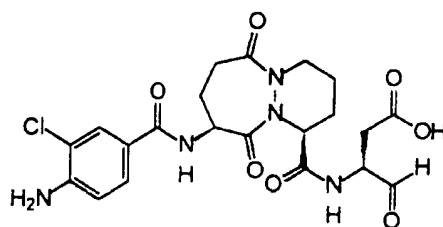
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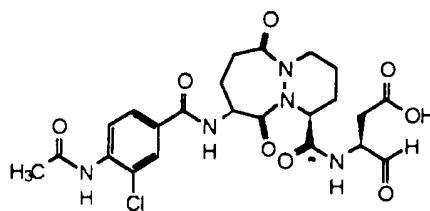
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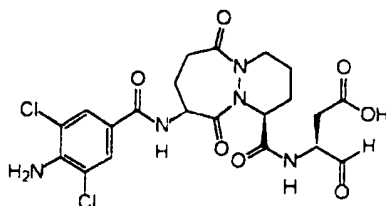
481



481s

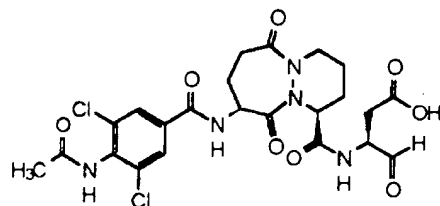


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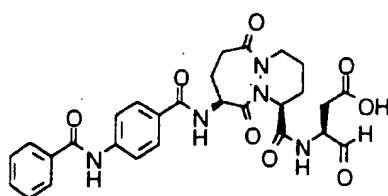


- 98 -

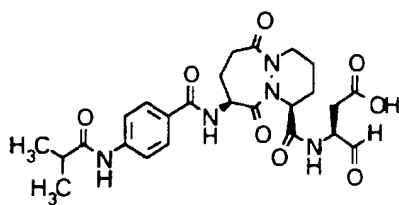
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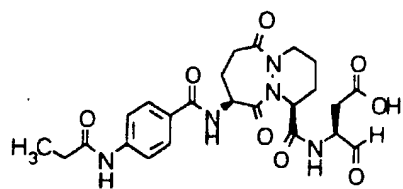
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484

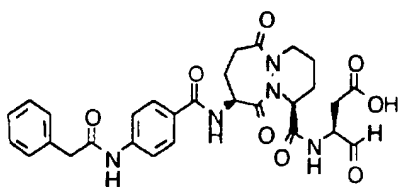


485



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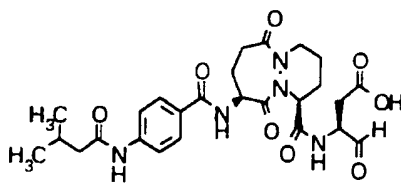
486



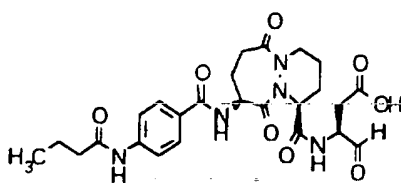


- 99 -

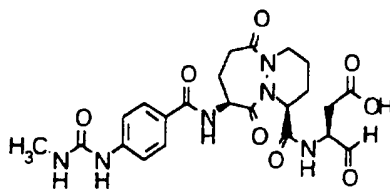
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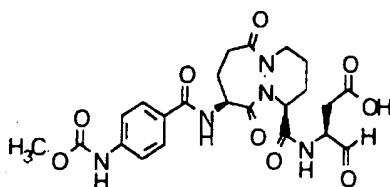
488



489

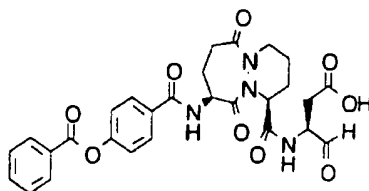


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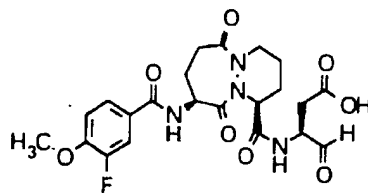
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491

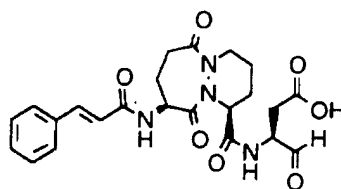


- 100 -

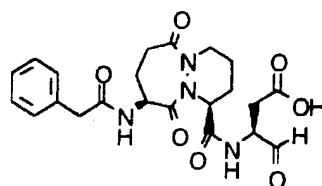
493



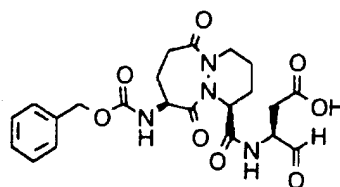
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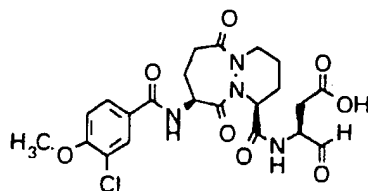


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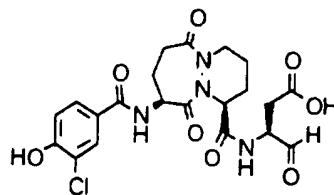
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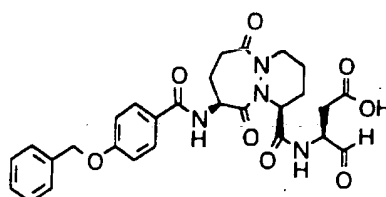


- 101 -

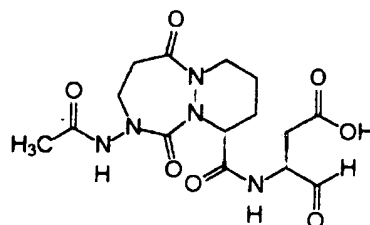
498



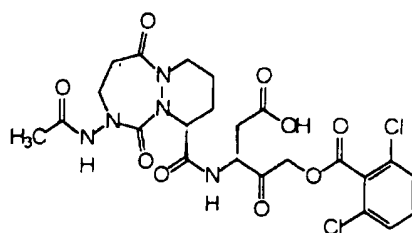
499



814c

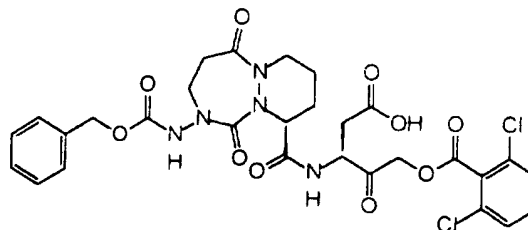


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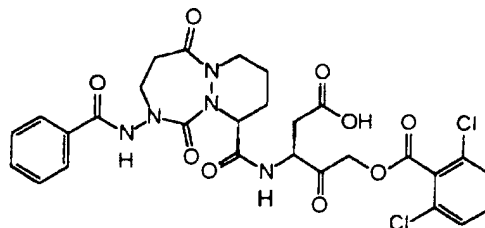
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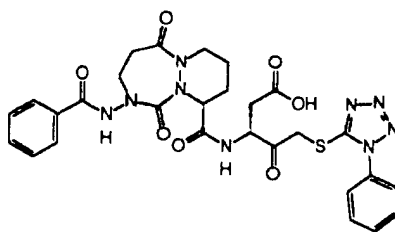


- 102 -

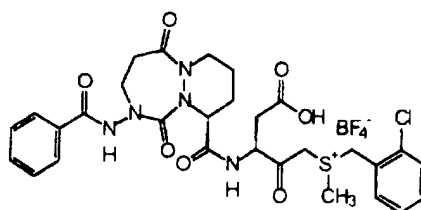
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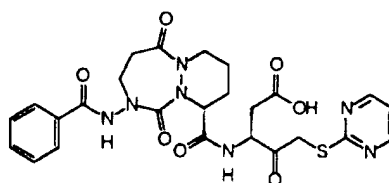
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881

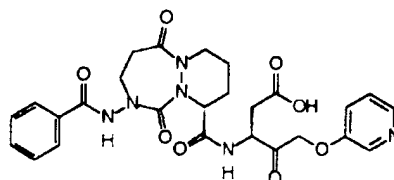


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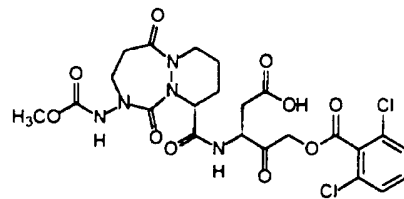
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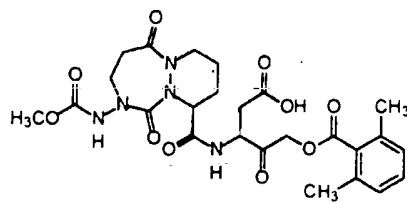


- 103 -

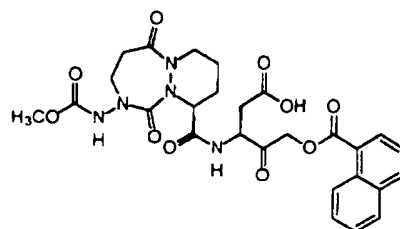
884



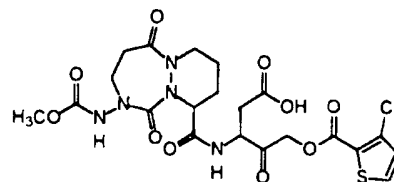
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886

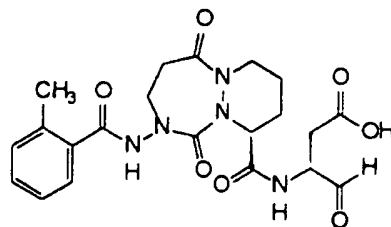


887



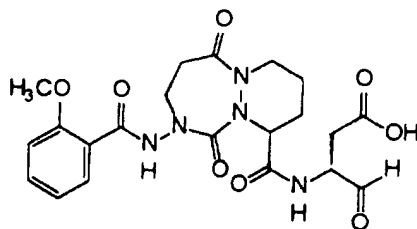
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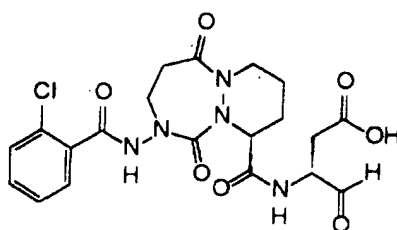


- 104 -

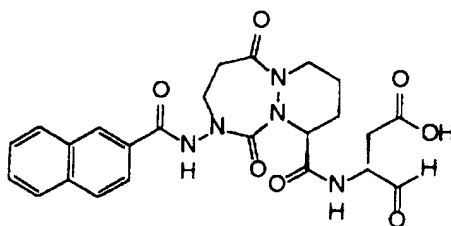
1005



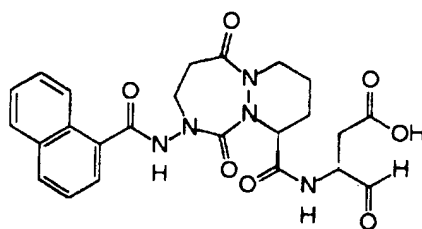
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1007

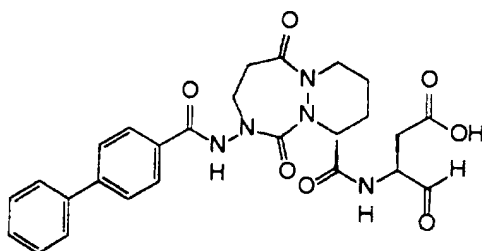


1008



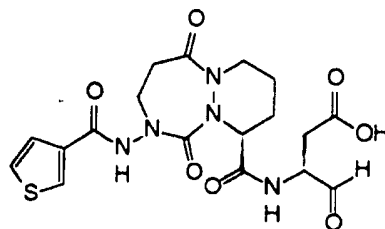
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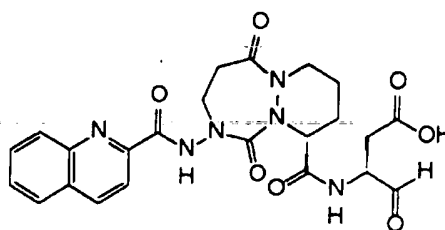


- 105 -

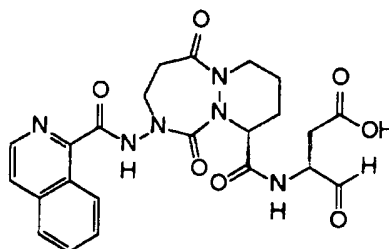
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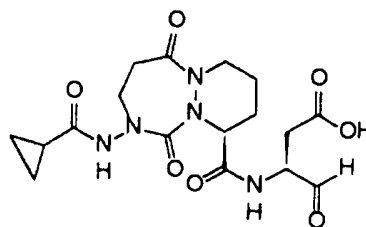
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1012

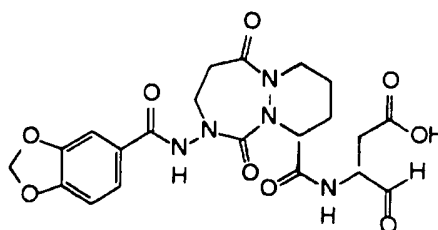


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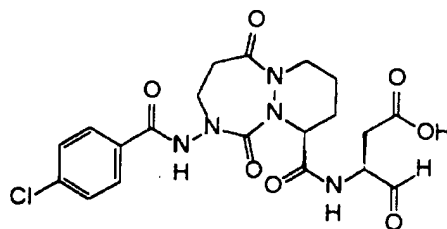
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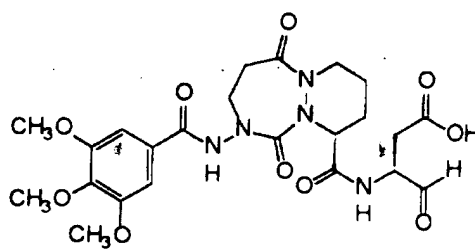


- 106 -

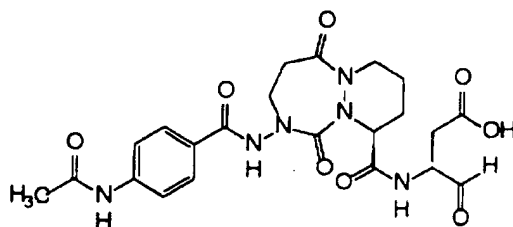
1016



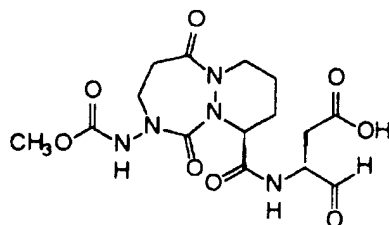
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1018

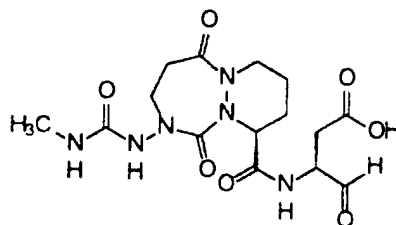


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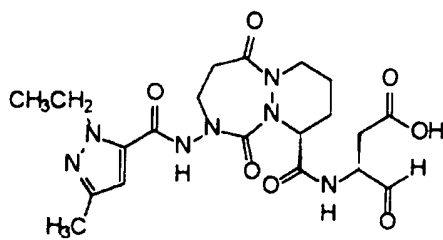


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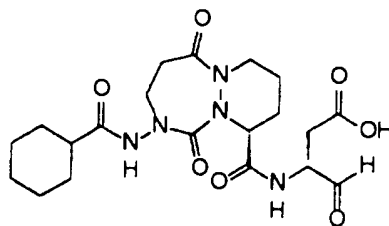
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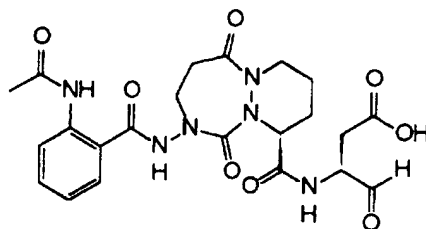
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1026

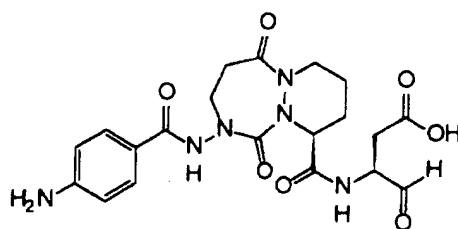


- 108 -

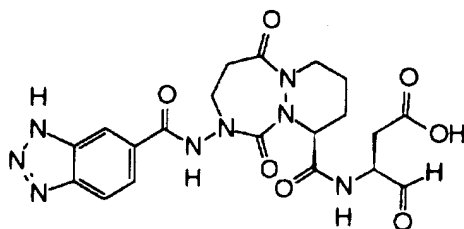
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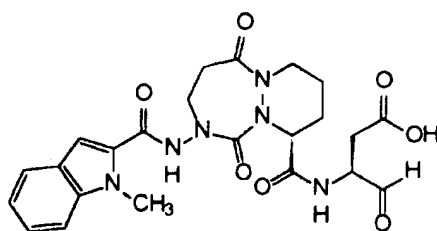
1031



1032

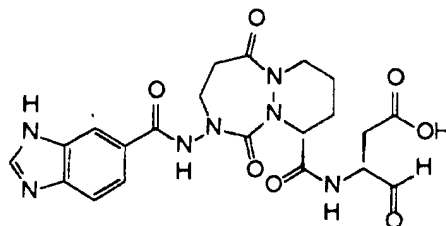


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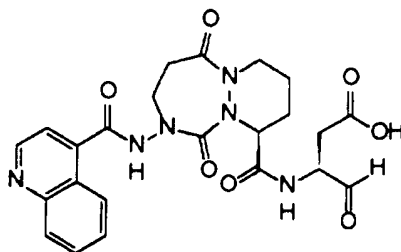
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1034

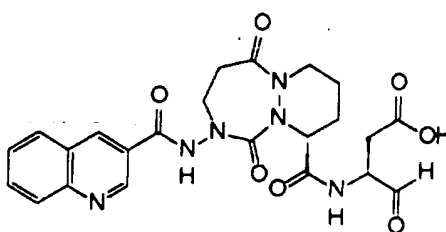


- 109 -

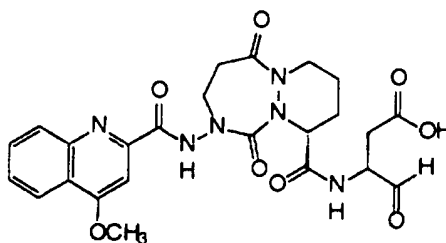
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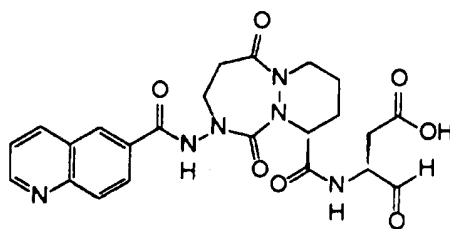
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1037

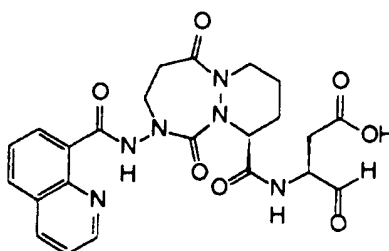


1038



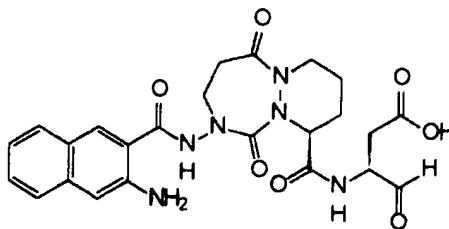
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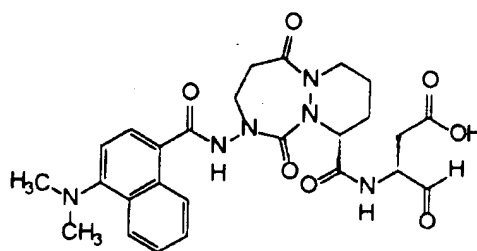


- 110 -

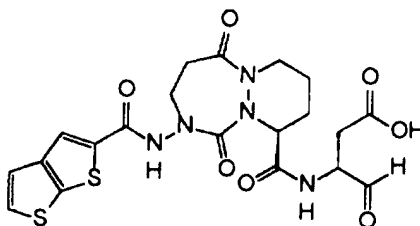
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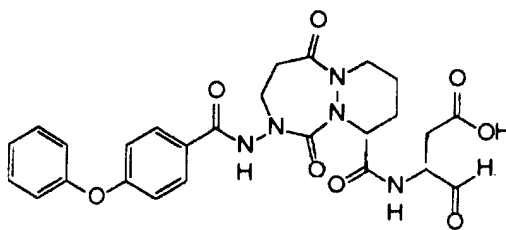
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1042

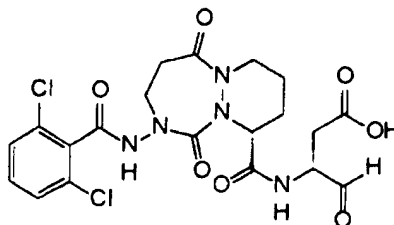


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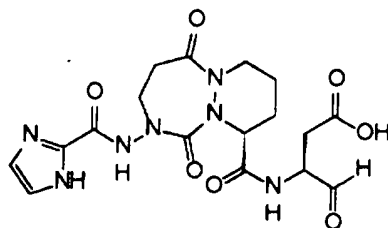
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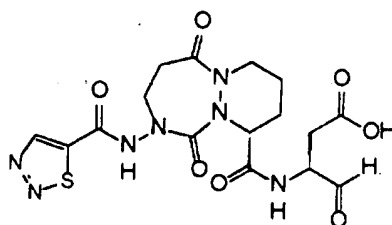


- 111 -

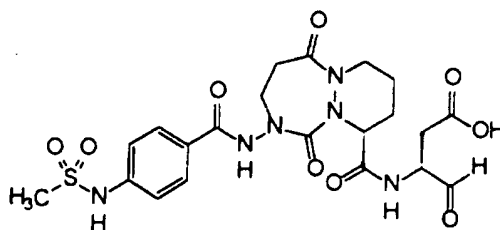
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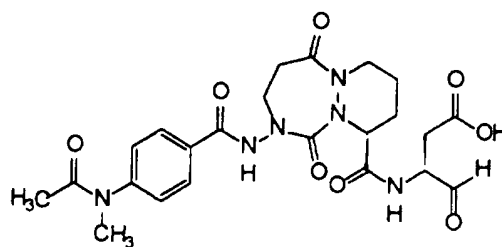
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1047

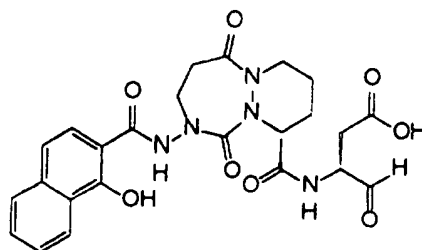


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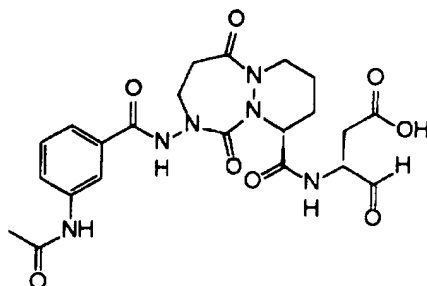
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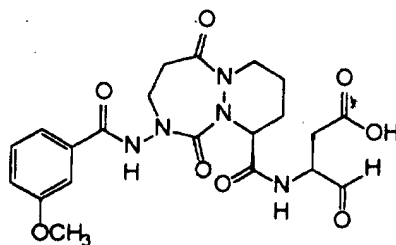


- 112 -

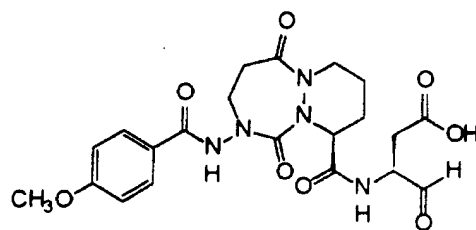
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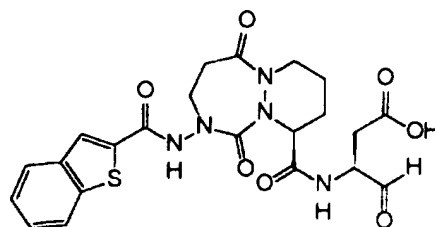
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1052

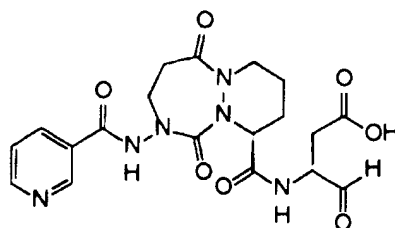


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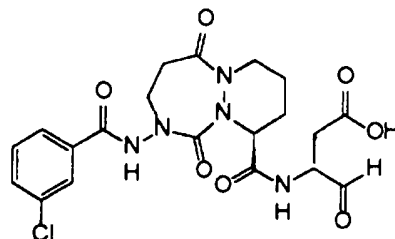
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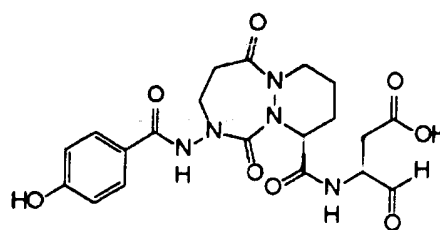


- 113 -

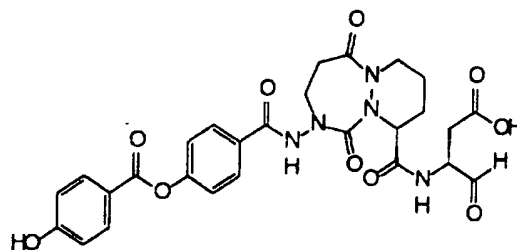
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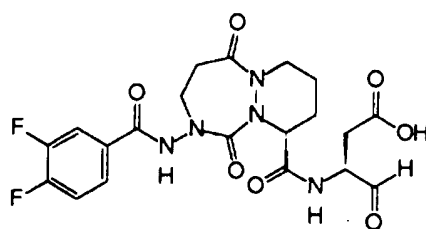
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1057

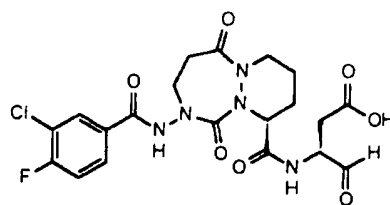


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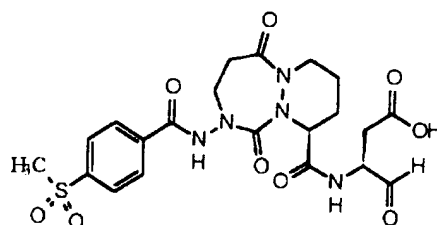
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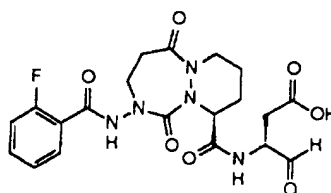


- 114 -

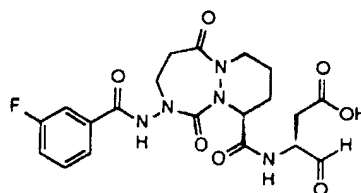
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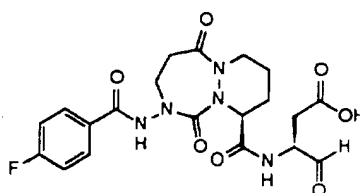
1061



1062

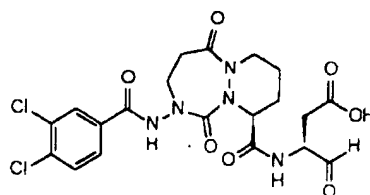


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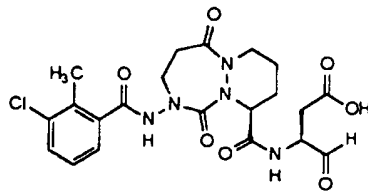
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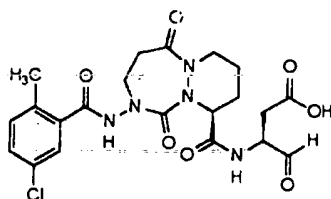


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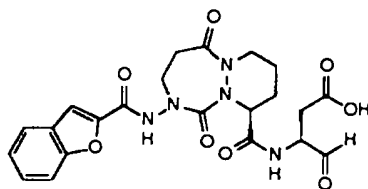
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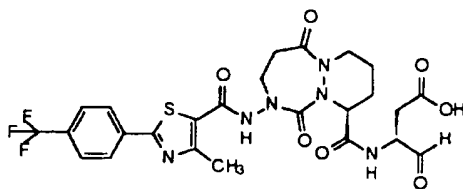
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1067

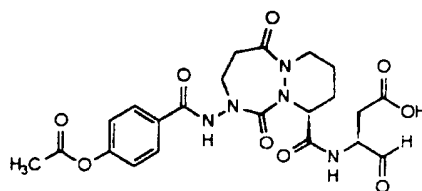


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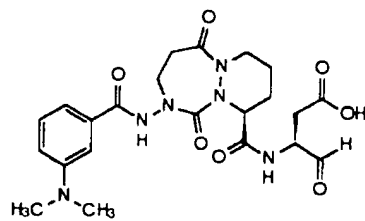
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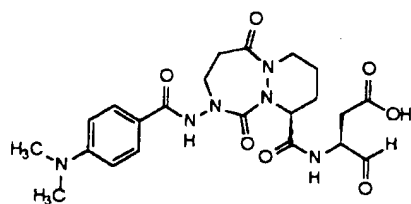


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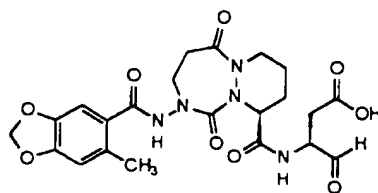
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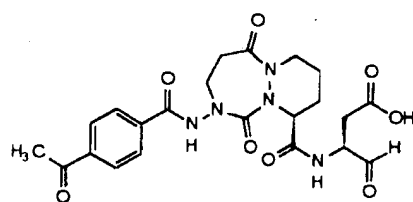
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1073

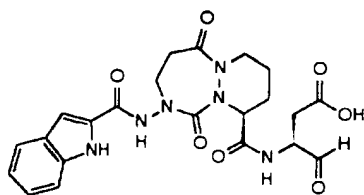


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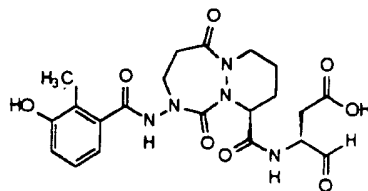
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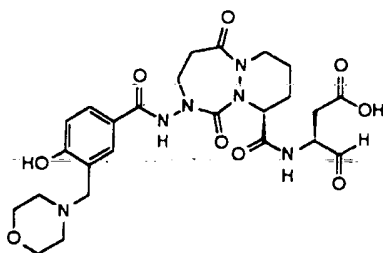


- 117 -

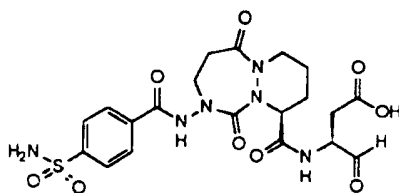
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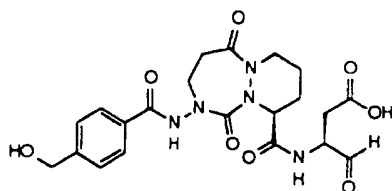
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1078

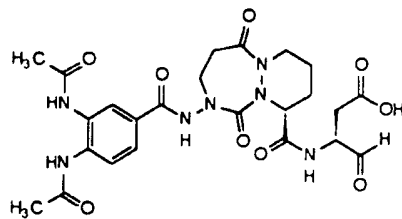


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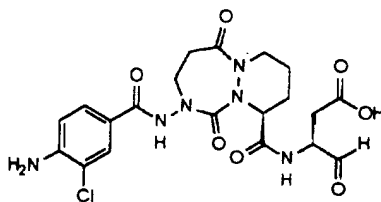
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1080

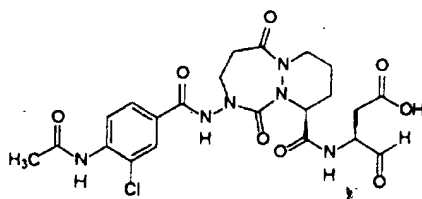


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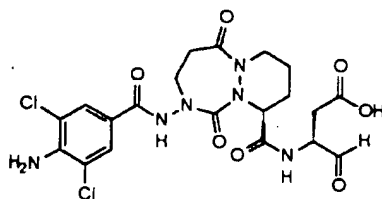
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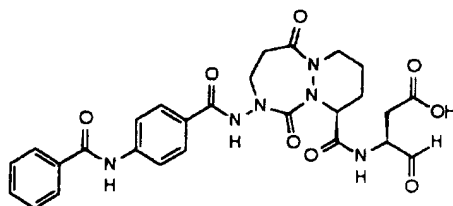
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1082

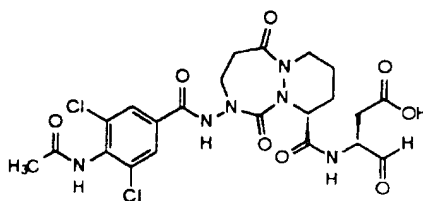


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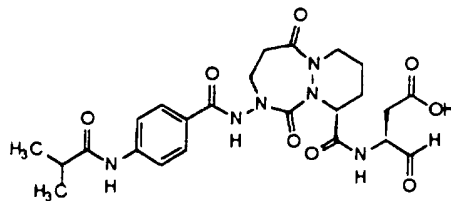
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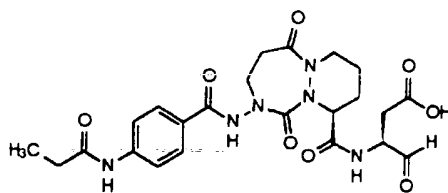


- 119 -

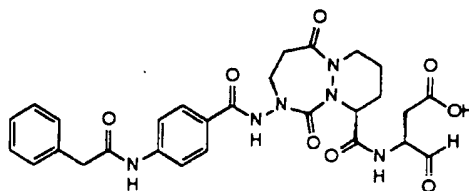
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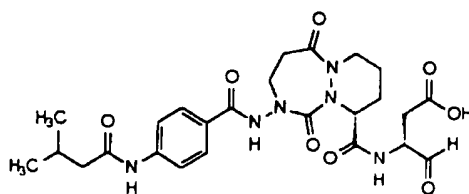
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1086

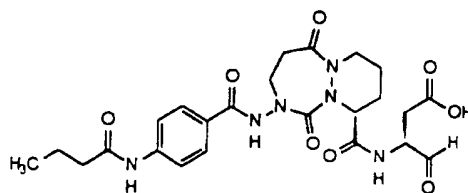


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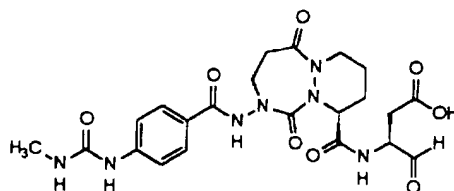
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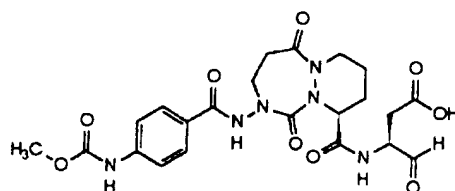


- 120 -

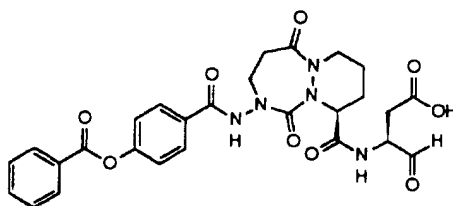
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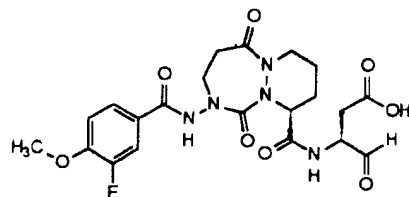
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1091

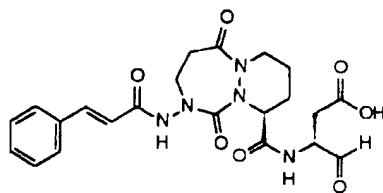


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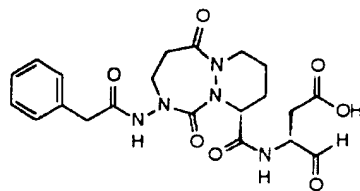


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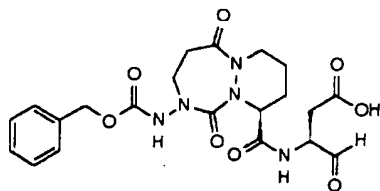


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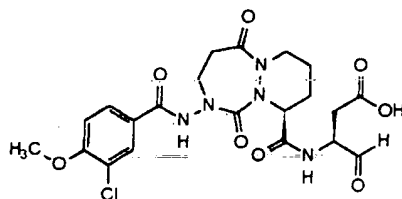


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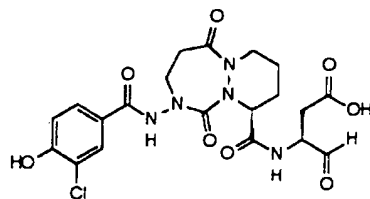
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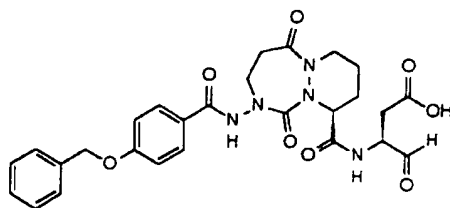
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1098

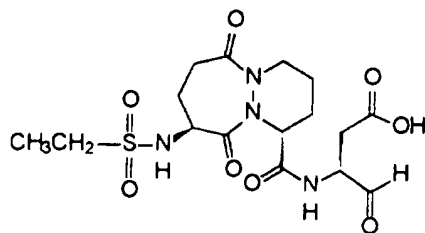


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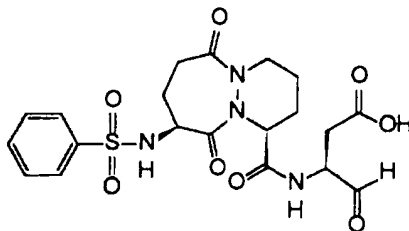
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421

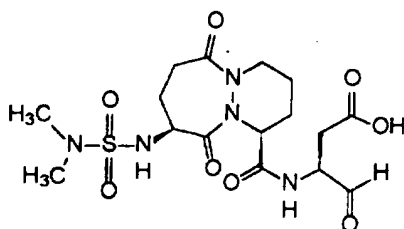


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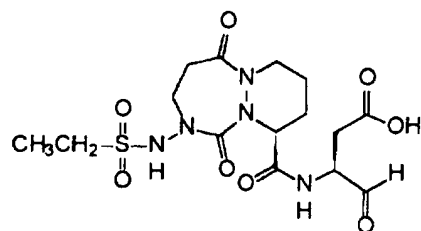
427



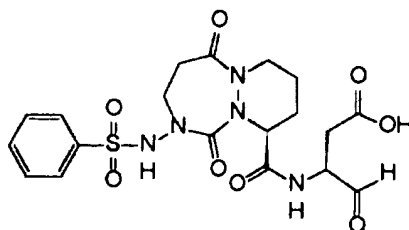
428



1021

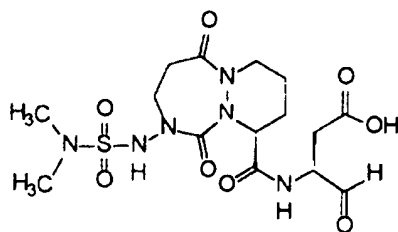


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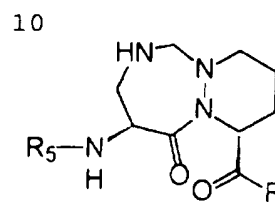
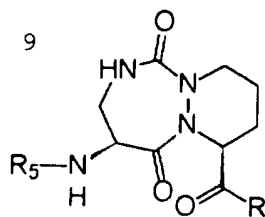
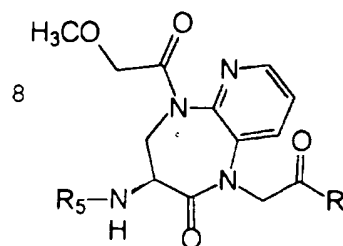
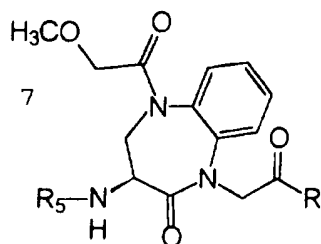
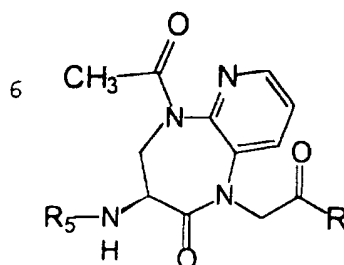
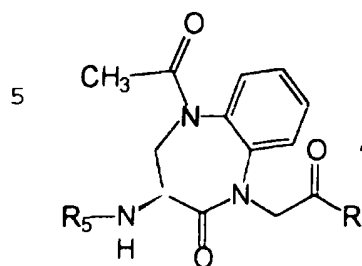
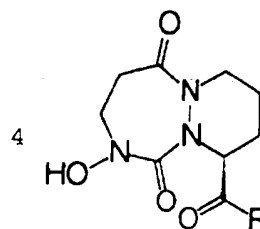
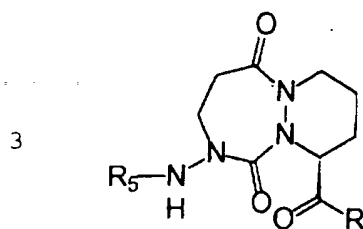
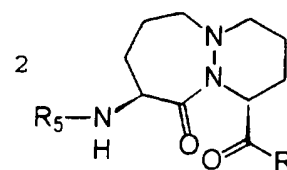
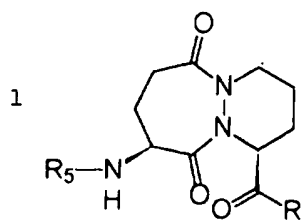
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1028

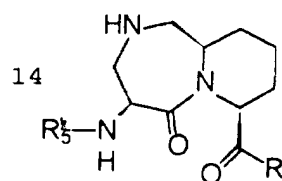
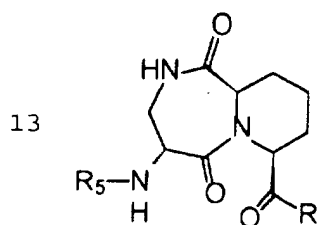
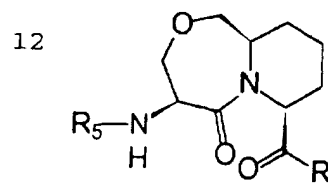
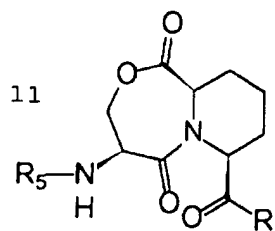


Specific compounds of this invention also include, but are not limited to, those compounds whose structures comprise scaffolds 1-22:

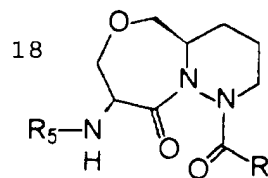
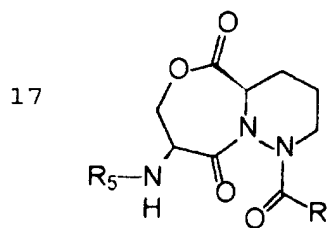
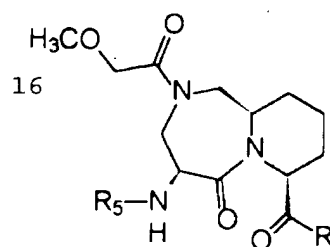
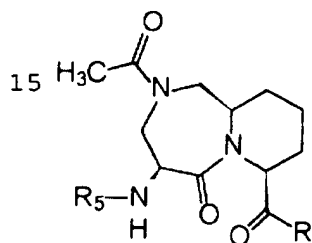




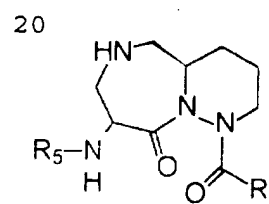
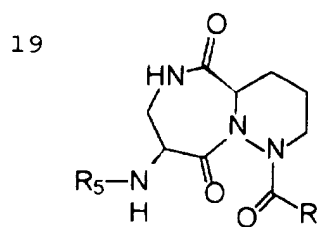
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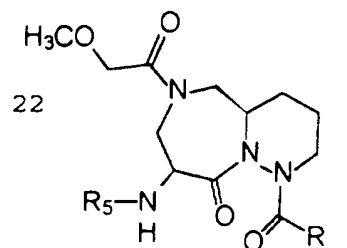
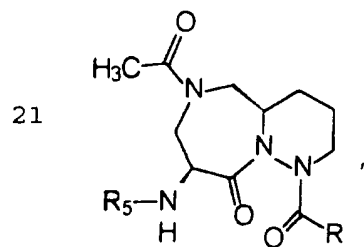
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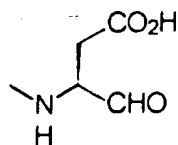


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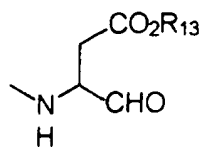


wherein:

R is



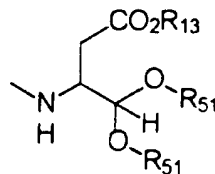
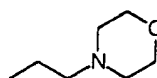
5



, wherein

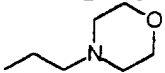
$R_{13}$  is  $-\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $-\text{CH}(\text{CH}_3)(\text{CH}_3)$ ,  
 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $-\text{CH}_2-\text{CH}(\text{CH}_3)\text{CH}_3$ ,  $-\text{C}(\text{CH}_3)_3$ ,  $-\text{CH}_2\text{Ph}$ , or

10



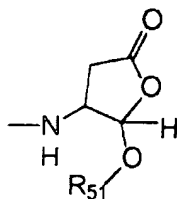
, wherein

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$R_{13}$  is  $-\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $-\text{CH}(\text{CH}_3)(\text{CH}_3)$ ,  
 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $-\text{CH}_2-\text{CH}(\text{CH}_3)\text{CH}_3$ ,  $-\text{C}(\text{CH}_3)_3$ ,  $-\text{CH}_2\text{Ph}$ ,  
 or , and

each  $R_{51}$  is  $-\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_3$ ,  
 5  $-\text{CH}(\text{CH}_3)(\text{CH}_3)$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $-\text{CH}_2-\text{CH}(\text{CH}_3)\text{CH}_3$ ,  $-\text{C}(\text{CH}_3)_3$ ,  
 $-\text{CH}_2\text{Ph}$ , or taken together form a ethylenedioxy acetal  
 or a propylenedioxy acetal; or

10



, wherein

$R_{51}$  is  $-\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $-\text{CH}(\text{CH}_3)(\text{CH}_3)$ ,  
 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $-\text{CH}_2-\text{CH}(\text{CH}_3)\text{CH}_3$ ,  $-\text{C}(\text{CH}_3)_3$ ,  $-\text{CH}_2\text{Ph}$ ,  
 $-\text{C}(\text{O})-\text{CH}_3$  or  $-\text{C}(\text{O})-\text{Ph}$ ;

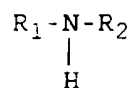
15  $R_5$  in each of the above compounds is the same as  
 any one of the  $R_5$  moieties shown for any one of  
 compounds 139, 214c, 214e, 404-413, 415-491, 493-501.

Specific compounds of this invention also include,  
 but are not limited to, compounds comprising scaffolds  
 20 1-28, wherein  $R$ ,  $R_{51}$ , and  $R_5$  are as defined above, and  
 in which the  $-\text{C}(\text{O})-$  of the  $R_5$  moiety of any one of  
 compounds 214c, 214e, 404-413, 415-418, 422-426, 430-  
 456, 458-466, 468, 470-471, 473-491, 493, 495, 497-501  
 is replaced with  $-\text{CH}_2-$ ,  $-\text{C}(\text{O})\text{C}(\text{O})-$ , or  $-\text{CH}_2\text{C}(\text{O})\text{C}(\text{O})-$ .

25 The ICE inhibitors of another embodiment (D)  
 of this invention are those of formula (I):

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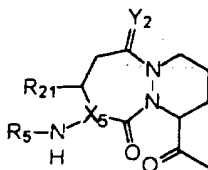
(I)



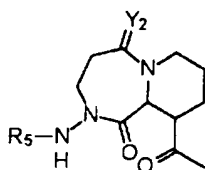
wherein:

5  $R_1$  is selected from the group consisting of the following formulae:

(e10)

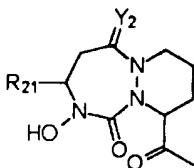


(e11)

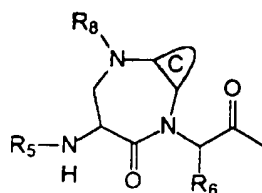


10

(e12)

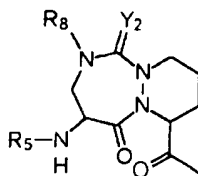


(w2)



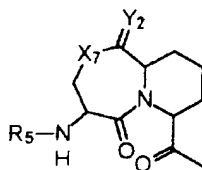
15

(y1)

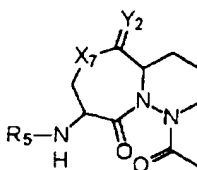


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(y2)



(z)

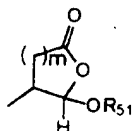


; and

ring C is chosen from the group consisting of  
 5 benzo, pyrido, thieno, pyrrolo, furano, thiazolo,  
 isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo,  
 cyclopentyl, and cyclohexyl;

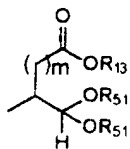
R<sub>2</sub> is:

(a)



, or

(b)



;

m is 1 or 2;

each R<sub>5</sub> is independently selected from the group  
 15 consisting of:

- C(O)-R<sub>10</sub>,
- C(O)O-R<sub>9</sub>,
- C(O)-N(R<sub>10</sub>)(R<sub>10</sub>)
- S(O)<sub>2</sub>-R<sub>9</sub>,

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5  
 -S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
 -C(O)-CH<sub>2</sub>-O-R<sub>9</sub>,  
 -C(O)C(O)-R<sub>10</sub>,  
 -R<sub>9</sub>,  
 -H,  
 -C(O)C(O)-OR<sub>10</sub>, and  
 -C(O)C(O)-N(R<sub>9</sub>)(R<sub>10</sub>);

10  
 X<sub>5</sub> is -CH- or -N-;

Y<sub>2</sub> is H<sub>2</sub> or O;

X<sub>7</sub> is -N(R<sub>8</sub>)- or -O-;

15  
 R<sub>6</sub> is selected from the group consisting of -H and  
 -CH<sub>3</sub>;

R<sub>8</sub> is selected from the group consisting of:

20  
 -C(O)-R<sub>10</sub>,  
 -C(O)O-R<sub>9</sub>,  
 -C(O)-N(H)-R<sub>10</sub>,  
 -S(O)<sub>2</sub>-R<sub>9</sub>,  
 -S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
 -C(O)-CH<sub>2</sub>-OR<sub>10</sub>,  
 -C(O)C(O)-R<sub>10</sub>;  
 25  
 -C(O)-CH<sub>2</sub>N(R<sub>10</sub>)(R<sub>10</sub>),  
 -C(O)-CH<sub>2</sub>C(O)-O-R<sub>9</sub>,  
 -C(O)-CH<sub>2</sub>C(O)-R<sub>9</sub>,  
 -H, and  
 -C(O)-C(O)-OR<sub>10</sub>;

30  
 each R<sub>9</sub> is independently selected from the group  
 consisting of -Ar<sub>3</sub> and a -C<sub>1-6</sub> straight or branched  
 alkyl group optionally substituted with Ar<sub>3</sub>, wherein

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the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

each R<sub>10</sub> is independently selected from the group consisting of -H, -Ar<sub>3</sub>, a C<sub>3-6</sub> cycloalkyl group, and a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, wherein the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

R<sub>13</sub> is selected from the group consisting of H, Ar<sub>3</sub>, and a C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, -CONH<sub>2</sub>, -OR<sub>5</sub>, -OH, -OR<sub>9</sub>, or -CO<sub>2</sub>H;

each R<sub>51</sub> is independently selected from the group consisting of R<sub>9</sub>, -C(O)-R<sub>9</sub>, -C(O)-N(H)-R<sub>9</sub>, or each R<sub>51</sub> taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-;

each R<sub>21</sub> is independently selected from the group consisting of -H or a -C<sub>1-6</sub> straight or branched alkyl group;

each Ar<sub>3</sub> is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Q<sub>1</sub> is independently selected from the group



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consisting of  $-\text{NH}_2$ ,  $-\text{CO}_2\text{H}$ ,  $-\text{Cl}$ ,  $-\text{F}$ ,  $-\text{Br}$ ,  $-\text{I}$ ,  $-\text{NO}_2$ ,  $-\text{CN}$ ,  
 $=\text{O}$ ,  $-\text{OH}$ ,  $-\text{perfluoro C}_{1-3}$  alkyl,  $\text{R}_5$ ,  $-\text{OR}_5$ ,  $-\text{NHR}_5$ ,  $\text{OR}_9$ ,  
 $-\text{N}(\text{R}_9)(\text{R}_{10})$ ,  $\text{R}_9$ ,  $-\text{C}(\text{O})-\text{R}_{10}$ , and



10 provided that when  $-\text{Ar}_3$  is substituted with a  $\text{Q}_1$  group which comprises one or more additional  $-\text{Ar}_3$  groups, said additional  $-\text{Ar}_3$  groups are not substituted with another  $-\text{Ar}_3$ .

Preferably,  $\text{R}_5$  is selected from the group  
 15 consisting of:  
 $-\text{C}(\text{O})-\text{R}_{10}$ ,  
 $-\text{C}(\text{O})\text{O}-\text{R}_9$ , and  
 $-\text{C}(\text{O})-\text{NH}-\text{R}_{10}$ .

Alternatively,  $\text{R}_5$  is selected from the group  
 20 consisting of:  
 $-\text{S}(\text{O})_2-\text{R}_9$ ,  
 $-\text{S}(\text{O})_2-\text{NH}-\text{R}_{10}$ ,  
 $-\text{C}(\text{O})-\text{C}(\text{O})-\text{R}_{10}$ ,  
 $-\text{R}_9$ , and  
 25  $-\text{C}(\text{O})-\text{C}(\text{O})-\text{OR}_{10}$ .

More preferably:

$m$  is 1;

$\text{R}_{13}$  is H or a  $-\text{C}_{1-4}$  straight or branched alkyl group optionally substituted with  $-\text{Ar}_3$ ,  $-\text{OH}$ ,  $-\text{OR}_9$ , or  
 30  $-\text{CO}_2\text{H}$ , wherein the  $\text{R}_9$  is a  $-\text{C}_{1-4}$  branched or straight alkyl group, wherein  $\text{Ar}_3$  is morpholinyl or phenyl, wherein the phenyl is optionally substituted with  $\text{Q}_1$ ;

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$R_{21}$  is -H or -CH<sub>3</sub>;

$R_{51}$  is a C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, wherein Ar<sub>3</sub> is phenyl, optionally substituted by -Q<sub>1</sub>;

5

each Ar<sub>3</sub> cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

10

each Q<sub>1</sub> is independently selected from the group consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -N(R<sub>9</sub>)(R<sub>10</sub>), and

15



wherein each R<sub>9</sub> and R<sub>10</sub> are independently a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub> wherein Ar<sub>3</sub> is phenyl;

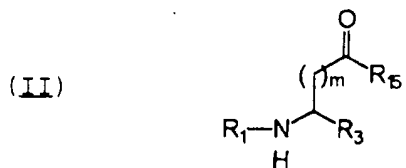
25

provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub> group which comprises one or more additional -Ar<sub>3</sub> groups, said additional -Ar<sub>3</sub> groups are not substituted with another -Ar<sub>3</sub>.

30

The ICE inhibitors of another embodiment (E) of this invention are those of formula (II):

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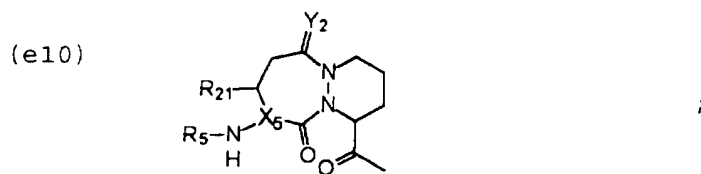


wherein:

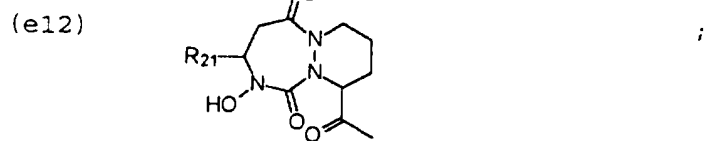
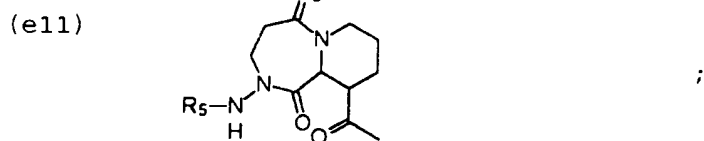
m is 1 or 2;

5

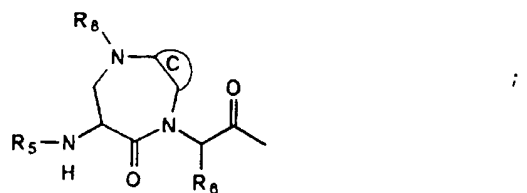
$R_1$  is selected from the group consisting of the following formulae:



10

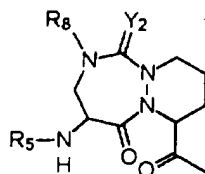


(w2)



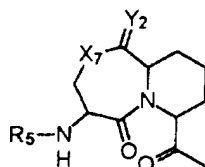
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(y1)



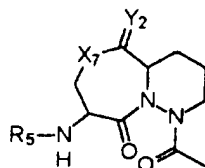
;

(y2)



;

(z)



; and

5

ring C is chosen from the group consisting of  
benzo, pyrido, thieno, pyrrolo, furano, thiazolo,  
isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo,  
10 cyclopentyl, and cyclohexyl;

R<sub>3</sub> is selected from the group consisting of:

- CN,
- C(O)-H,
- C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>,
- 15 -C(O)-CH<sub>2</sub>-F,
- C=N-O-R<sub>9</sub>, and
- CO-Ar<sub>2</sub>;

each R<sub>5</sub> is independently selected from the group  
consisting of:

20

- C(O)-R<sub>10</sub>,
- C(O)O-R<sub>9</sub>,
- C(O)-N(R<sub>10</sub>)(R<sub>10</sub>)
- S(O)<sub>2</sub>-R<sub>9</sub>,
- S(O)<sub>2</sub>-NH-R<sub>10</sub>,

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-C(O)-CH<sub>2</sub>-O-R<sub>9</sub>,  
 -C(O)C(O)-R<sub>10</sub>,  
 -R<sub>9</sub>,  
 -H,  
 -C(O)C(O)-OR<sub>10</sub>, and  
 -C(O)C(O)-N(R<sub>9</sub>)(R<sub>10</sub>);

X<sub>5</sub> is -CH- or -N-;  
 |                    |

Y<sub>2</sub> is H<sub>2</sub> or O;

X<sub>7</sub> is -N(R<sub>8</sub>)- or -O-;

each T<sub>1</sub> is independently selected from the group consisting of -O-, -S-, -S(O)-, and -S(O)<sub>2</sub>-;

R<sub>6</sub> is selected from the group consisting of -H and -CH<sub>3</sub>;

R<sub>8</sub> is selected from the group consisting of:

-C(O)-R<sub>10</sub>,  
 -C(O)O-R<sub>9</sub>,  
 -C(O)-NH-R<sub>10</sub>,  
 -S(O)<sub>2</sub>-R<sub>9</sub>,  
 -S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
 -C(O)-CH<sub>2</sub>-OR<sub>10</sub>,  
 -C(O)C(O)-R<sub>10</sub>,  
 -C(O)-CH<sub>2</sub>-N(R<sub>10</sub>)(R<sub>10</sub>),  
 -C(O)-CH<sub>2</sub>C(O)-O-R<sub>9</sub>,  
 -C(O)-CH<sub>2</sub>C(O)-R<sub>9</sub>,  
 -H, and  
 -C(O)-C(O)-OR<sub>10</sub>;

each R<sub>9</sub> is independently selected from the group consisting of -Ar<sub>3</sub> and a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, wherein

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the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

each R<sub>10</sub> is independently selected from the group consisting of -H, -Ar<sub>3</sub>, a C<sub>3-6</sub> cycloalkyl group, and a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, wherein the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

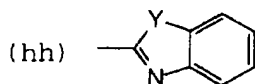
each R<sub>11</sub> is independently selected from the group consisting of:

-Ar<sub>4</sub>,  
-(CH<sub>2</sub>)<sub>1-3</sub>-Ar<sub>4</sub>,  
-H, and  
-C(O)-Ar<sub>4</sub>;

R<sub>15</sub> is selected from the group consisting of -OH, -OAr<sub>3</sub>, -N(H)-OH, and a -OC<sub>1-6</sub> straight or branched alkyl group optionally substituted with -Ar<sub>3</sub>, -CONH<sub>2</sub>, -OR<sub>5</sub>, -OH, -OR<sub>9</sub>, or -CO<sub>2</sub>H;

each R<sub>21</sub> is independently selected from the group consisting of -H or a -C<sub>1-6</sub> straight or branched alkyl group;

Ar<sub>2</sub> is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by -Q<sub>1</sub>:



, and

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(iii)



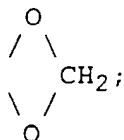
wherein each Y is independently selected from the group consisting of O and S;

5 each Ar<sub>3</sub> is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said  
10 heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, and -NH-, -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings,  
15 and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Ar<sub>4</sub> is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3  
20 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, -NH-, -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally  
25 containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Q<sub>1</sub> is independently selected from the group  
30 consisting of -NH<sub>2</sub>, -CO<sub>2</sub>H, -Cl, -F, -Br, -I, -NO<sub>2</sub>, -CN, =O, -OH, -perfluoro C<sub>1-3</sub> alkyl, R<sub>5</sub>, -OR<sub>5</sub>, -NHR<sub>5</sub>, OR<sub>9</sub>, -N(R<sub>9</sub>)(R<sub>10</sub>), R<sub>9</sub>, -C(O)-R<sub>10</sub>, and

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5 provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub> group which comprises one or more additional -Ar<sub>3</sub> groups, said additional -Ar<sub>3</sub> groups are not substituted  
10 with another -Ar<sub>3</sub>.

Preferred compounds of embodiment E employ formula (II), wherein R<sub>1</sub> is (e11) and the other substituents are as defined above.

15 Other preferred compounds of embodiment E employ formula (II), wherein R<sub>1</sub> is (e12) and the other substituents are as defined above.

Other preferred compounds of embodiment E employ formula (II) wherein R<sub>1</sub> is (y1) and the other substituents are as defined above.

20 Other preferred compounds of embodiment E employ formula (II) wherein R<sub>1</sub> is (y2) and the other substituents are as defined above.

Other preferred compounds of embodiment E of employ formula (II) wherein R<sub>1</sub> is (z) and the other  
25 substituents are as defined above.

Other preferred compound of embodiment E employ formula (II) wherein R<sub>1</sub> is (w2) and the other substituents are as defined above.

More preferably, R<sub>1</sub> is (w2) and



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m is 1;

ring C is benzo, pyrido, or thieno;

R<sub>3</sub> is selected from the group consisting of  
-C(O)-H, -C(O)-Ar<sub>2</sub>, and -C(O)CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>;

5 R<sub>5</sub> is selected from the group consisting of:  
-C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is -Ar<sub>3</sub>;  
-C(O)O-R<sub>9</sub>, wherein R<sub>9</sub> is -CH<sub>2</sub>-Ar<sub>3</sub>;  
-C(O)C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is -Ar<sub>3</sub>;  
-R<sub>9</sub>, wherein R<sub>9</sub> is a C<sub>1-2</sub> alkyl group  
10 substituted with -Ar<sub>3</sub>; and  
-C(O)C(O)-OR<sub>10</sub>, wherein R<sub>10</sub> is -CH<sub>2</sub>Ar<sub>3</sub>;

T<sub>1</sub> is O or S;

R<sub>6</sub> is H;

15 R<sub>8</sub> is selected from the group consisting -C(O)-R<sub>10</sub>,  
-C(O)-CH<sub>2</sub>-OR<sub>10</sub>, and -C(O)CH<sub>2</sub>-N(R<sub>10</sub>)(R<sub>10</sub>), wherein R<sub>10</sub> is  
H, CH<sub>3</sub>, or -CH<sub>2</sub>CH<sub>3</sub>;

R<sub>11</sub> is selected from the group consisting of -Ar<sub>4</sub>,  
-(CH<sub>2</sub>)<sub>1-3</sub>-Ar<sub>4</sub>, and -C(O)-Ar<sub>4</sub>;

20 R<sub>15</sub> is -OH or -OC<sub>1-4</sub> straight or branched alkyl  
group optionally substituted with -Ar<sub>3</sub>, -OH, -OR<sub>9</sub>, or  
-CO<sub>2</sub>H, wherein the R<sub>9</sub> is a -C<sub>1-4</sub> branched or straight  
alkyl group, wherein Ar<sub>3</sub> is morpholinyl or phenyl,  
wherein the phenyl is optionally substituted with Q<sub>1</sub>;

25 Ar<sub>2</sub> is (hh);

Y is O;

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each Ar<sub>3</sub> cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, thiazolyl, benzimidazolyl, thienothienyl, thiadiazolyl, benzotriazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Ar<sub>4</sub> cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, naphthyl, pyridinyl, oxazolyl, pyrimidinyl, or indolyl, said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Q<sub>1</sub> is independently selected from the group consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -N(R<sub>9</sub>)(R<sub>10</sub>), and



wherein each R<sub>9</sub> and R<sub>10</sub> are independently a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub> wherein Ar<sub>3</sub> is phenyl;

provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub> group which comprises one or more additional -Ar<sub>3</sub> groups, said additional -Ar<sub>3</sub> groups are not substituted with another -Ar<sub>3</sub>.

Other preferred compounds of embodiment E employ formula (II) wherein R<sub>1</sub> is (e10), X<sub>5</sub> is CH, and the other substituents are as defined above.

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More preferred compounds of embodiment E employ formula (II) wherein  $R_1$  is (e10),  $X_5$  is CH,  $R_3$  is CO-Ar<sub>2</sub>, and the other substituents are as defined above.

5 Other more preferred compounds of embodiment E employ formula (II) wherein  $R_1$  is (e10),  $X_5$  is CH,  $R_3$  is -C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>,  $R_{11}$  is -(CH<sub>2</sub>)<sub>1-3</sub>-Ar<sub>4</sub>, and the other substituents are as defined above.

10 Other more preferred compounds of embodiment E employ formula (II) wherein  $R_1$  is (e10) and  $X_5$  is CH and  $R_3$  is -C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>, T<sub>1</sub> is O,  $R_{11}$  is -C(O)-Ar<sub>4</sub>, and the other substituents are as defined above.

More preferably, in these more preferred compounds,  $R_5$  is selected from the group consisting of:

15 -C(O)-R<sub>10</sub>,  
-C(O)O-R<sub>9</sub>, and  
-C(O)-NH-R<sub>10</sub>.

Alternatively, in these more preferred compounds,  $R_5$  is selected from the group consisting of:

20 -S(O)<sub>2</sub>-R<sub>9</sub>,  
-S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
-C(O)-C(O)-R<sub>10</sub>,  
-R<sub>9</sub>, and  
-C(O)-C(O)-OR<sub>10</sub>.

25 Most preferably, in these more preferred compounds,

m is 1;

T<sub>1</sub> is O or S;

R<sub>15</sub> is -OH or -OC<sub>1-4</sub> straight or branched alkyl

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group optionally substituted with  $-\text{Ar}_3$ ,  $-\text{OH}$ ,  $-\text{OR}_9$ , or  $-\text{CO}_2\text{H}$ , wherein the  $\text{R}_9$  is a  $-\text{C}_{1-4}$  branched or straight alkyl group, wherein  $\text{Ar}_3$  is morpholinyl or phenyl, wherein the phenyl is optionally substituted with  $\text{Q}_1$ ;

5  $\text{R}_{21}$  is  $-\text{H}$  or  $-\text{CH}_3$ ;

$\text{Ar}_2$  is (hh);

$\text{Y}$  is  $\text{O}$ , and

each  $\text{Ar}_3$  cyclic group is independently selected  
 10 from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl,  
 15 and said cyclic group optionally being singly or multiply substituted by  $-\text{Q}_1$ ;

each  $\text{Ar}_4$  cyclic group is independently selected  
 from the set consisting of phenyl, tetrazolyl,  
 pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl,  
 20 said cyclic group being singly or multiply substituted by  $-\text{Q}_1$ ;

each  $\text{Q}_1$  is independently selected from the group  
 consisting of  $-\text{NH}_2$ ,  $-\text{Cl}$ ,  $-\text{F}$ ,  $-\text{Br}$ ,  $-\text{OH}$ ,  $-\text{R}_9$ ,  $-\text{NH}-\text{R}_5$   
 wherein  $\text{R}_5$  is  $-\text{C}(\text{O})-\text{R}_{10}$  or  $-\text{S}(\text{O})_2-\text{R}_9$ ,  $-\text{OR}_5$  wherein  $\text{R}_5$  is  
 25  $-\text{C}(\text{O})-\text{R}_{10}$ ,  $-\text{OR}_9$ ,  $-\text{N}(\text{R}_9)(\text{R}_{10})$ , and



wherein each  $\text{R}_9$  and  $\text{R}_{10}$  are independently a  $-\text{C}_{1-6}$

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straight or branched alkyl group optionally substituted with Ar<sub>3</sub> wherein Ar<sub>3</sub> is phenyl;

5 provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub> group which comprises one or more additional -Ar<sub>3</sub> groups, said additional -Ar<sub>3</sub> groups are not substituted with another -Ar<sub>3</sub>.

10 Other more preferred compounds of embodiment E employ formula (II) wherein R<sub>1</sub> is (e10), X<sub>5</sub> is CH, R<sub>3</sub> is -C(O)-H, and the other substituents are as defined above.

More preferably, in these more preferred compounds, R<sub>5</sub> is selected from the group consisting of:

15 -C(O)-R<sub>10</sub>,  
-C(O)O-R<sub>9</sub>, and  
-C(O)-NH-R<sub>10</sub>.

Alternatively, in these more preferred compounds, R<sub>5</sub> is selected from the group consisting of:

20 -S(O)<sub>2</sub>-R<sub>9</sub>,  
-S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
-C(O)-C(O)-R<sub>10</sub>,  
-R<sub>9</sub>, and  
-C(O)-C(O)-OR<sub>10</sub>.

Most preferably, in these more preferred compounds,

25 m is 1;

30 R<sub>15</sub> is -OH or -OC<sub>1-4</sub> straight or branched alkyl group optionally substituted with -Ar<sub>3</sub>, -OH, -OR<sub>9</sub>, or -CO<sub>2</sub>H, wherein the R<sub>9</sub> is a -C<sub>1-4</sub> branched or straight alkyl group, wherein Ar<sub>3</sub> is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q<sub>1</sub>;

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R<sub>21</sub> is -H or -CH<sub>3</sub>;

each Ar<sub>3</sub> cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Q<sub>1</sub> is independently selected from the group consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -N(R<sub>9</sub>)(R<sub>10</sub>), and



20 wherein each R<sub>9</sub> and R<sub>10</sub> are independently a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub> wherein Ar<sub>3</sub> is phenyl;

25 provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub> group which comprises one or more additional -Ar<sub>3</sub> groups, said additional -Ar<sub>3</sub> groups are not substituted with another -Ar<sub>3</sub>,

30 Other more preferred compounds of embodiment E employ formula (II) wherein R<sub>1</sub> is (e10) and X<sub>5</sub> is CH, R<sub>3</sub> is -CO-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>, and R<sub>11</sub> is -Ar<sub>4</sub>, and the other substituents are as defined above.

More preferably, in these more preferred compounds, R<sub>5</sub> is selected from the group consisting of:

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-C(O)-R<sub>10</sub>,  
-C(O)O-R<sub>9</sub>, and  
-C(O)-NH-R<sub>10</sub>.

Alternatively, in these more preferred compounds, R<sub>5</sub> is  
5 selected from the group consisting of:

-S(O)<sub>2</sub>-R<sub>9</sub>,  
-S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
-C(O)-C(O)-R<sub>10</sub>,  
-R<sub>9</sub>, and  
10 -C(O)-C(O)-OR<sub>10</sub>.

Most preferably, in these more preferred compounds,

m is 1;

T<sub>1</sub> is O or S;

15 R<sub>15</sub> is -OH or a -OC<sub>1-4</sub> straight or branched alkyl  
group optionally substituted with -Ar<sub>3</sub>, -OH, -OR<sub>9</sub>, or  
-CO<sub>2</sub>H, wherein the R<sub>9</sub> is a -C<sub>1-4</sub> branched or straight  
alkyl group, wherein Ar<sub>3</sub> is morpholinyl or phenyl,  
wherein the phenyl is optionally substituted with Q<sub>1</sub>;

20 R<sub>21</sub> is -H or -CH<sub>3</sub>;

each Ar<sub>3</sub> cyclic group is phenyl, naphthyl,  
thienyl, quinolinyl, isoquinolinyl, pyrazolyl,  
thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl,  
25 thienothienyl, imidazolyl, thiadiazolyl,  
benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl,  
and said cyclic group optionally being singly or  
multiply substituted by -Q<sub>1</sub>;

each Ar<sub>4</sub> cyclic group is independently selected

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from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl, said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

- 5 each  $Q_1$  is independently selected from the group consisting of  $-NH_2$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-OH$ ,  $-R_9$ ,  $-NH-R_5$  wherein  $R_5$  is  $-C(O)-R_{10}$  or  $-S(O)_2-R_9$ ,  $-OR_5$  wherein  $R_5$  is  $-C(O)-R_{10}$ ,  $-OR_9$ ,  $-N(R_9)(R_{10})$ , and



- wherein each  $R_9$  and  $R_{10}$  are independently a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$  wherein  $Ar_3$  is phenyl;
- 15

- provided that when  $-Ar_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-Ar_3$  groups, said additional  $-Ar_3$  groups are not substituted with another  $-Ar_3$ .
- 20

Other preferred compounds of embodiment E employ formula (II) wherein  $R_1$  is (e10),  $X_5$  is N, and the other substituents are as defined above.

- 25 More preferred compounds of embodiment E, employ formula (II) wherein  $R_1$  is (e10),  $X_5$  is N,  $R_3$  is  $CO-Ar_2$ , and the other substituents are as defined above.

- Other more preferred compounds of embodiment E, employ formula (II) wherein  $R_1$  is (e10),  $X_5$  is N,  $R_3$  is  $-C(O)-CH_2-T_1-R_{11}$ ,  $R_{11}$  is  $-(CH_2)_{1-3}-Ar_4$ , and the other substituents are as defined above.
- 30



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Other more preferred compounds of embodiment E, employ formula (II) wherein  $R_1$  is (e10) and  $X_5$  is N and:

5            $R_3$  is  $-C(O)-CH_2-T_1-R_{11}$ ;  
             $T_1$  is O; and  
             $R_{11}$  is  $-C(O)-Ar_4$ , and the other substituents are as defined above.

More preferably, in these more preferred compounds,  $R_5$  is selected from the group consisting of:

10            $-C(O)-R_{10}$ ,  
             $-C(O)O-R_9$ , and  
             $-C(O)-NH-R_{10}$ .

Alternatively, in these more preferred compounds,  $R_5$  is selected from the group consisting of:

15            $-S(O)_2-R_9$ ,  
             $-S(O)_2-NH-R_{10}$ ,  
             $-C(O)-C(O)-R_{10}$ ,  
             $-R_9$ , and  
20            $-C(O)-C(O)-OR_{10}$ .

Most preferably, in these more preferred compounds,  
 $m$  is 1;

$T_1$  is O or S;

25            $R_{15}$  is  $-OH$  or a  $-OC_{1-4}$  straight or branched alkyl group optionally substituted with  $-Ar_3$ ,  $-OH$ ,  $-OR_9$ , or  $-CO_2H$ , wherein the  $R_9$  is a  $-C_{1-4}$  branched or straight alkyl group, wherein  $Ar_3$  is morpholinyl or phenyl, wherein the phenyl is optionally substituted with  $Q_1$ ;

30            $R_{21}$  is  $-H$  or  $-CH_3$ ;

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Ar<sub>2</sub> is (hh);

Y is O, and

each Ar<sub>3</sub> cyclic group is independently selected  
 5 from the set consisting of phenyl, naphthyl, thienyl,  
 quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl,  
 isoxazolyl, benzotriazolyl, benzimidazolyl,  
 thienothienyl, imidazolyl, thiadiazolyl,  
 benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl,  
 10 and said cyclic group optionally being singly or  
 multiply substituted by -Q<sub>1</sub>;

each Ar<sub>4</sub> cyclic group is independently selected  
 from the set consisting of phenyl, tetrazolyl,  
 pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl,  
 15 optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Q<sub>1</sub> is independently selected from the group  
 consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub>  
 wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is  
 -C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -N(R<sub>9</sub>)(R<sub>10</sub>), and



25 wherein each R<sub>9</sub> and R<sub>10</sub> are independently a -C<sub>1-6</sub>  
 straight or branched alkyl group optionally substituted  
 with Ar<sub>3</sub> wherein Ar<sub>3</sub> is phenyl;

provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub>  
 30 group which comprises one or more additional -Ar<sub>3</sub>  
 groups, said additional -Ar<sub>3</sub> groups are not substituted  
 with another -Ar<sub>3</sub>.

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Other more preferred compounds of embodiment E, employ formula (II) wherein  $R_1$  is (e10),  $X_5$  is N,  $R_3$  is  $-C(O)-H$ , and the other substituents are as defined above.

5 More preferably, in these more preferred compounds,  $R_5$  is selected from the group consisting of:

$-C(O)-R_{10}$ ,  
 $-C(O)O-R_9$ , and  
 $-C(O)-NH-R_{10}$ .

10 Alternatively, in these more preferred compounds,  $R_5$  is selected from the group consisting of:

$-S(O)_2-R_9$ ,  
 $-S(O)_2-NH-R_{10}$ ,  
 $-C(O)-C(O)-R_{10}$ ,

15  $-R_9$ , and  
 $-C(O)-C(O)-OR_{10}$ .

Most preferably, in these more preferred compounds,

$m$  is 1;

20  $R_{15}$  is  $-OH$  or  $-OC_{1-4}$  straight or branched alkyl group optionally substituted with  $-Ar_3$ ,  $-OH$ ,  $-OR_9$ , or  $-CO_2H$ , wherein the  $R_9$  is a  $-C_{1-4}$  branched or straight alkyl group, wherein  $Ar_3$  is morpholinyl or phenyl, wherein the phenyl is optionally substituted with  $Q_1$ ;

$R_{21}$  is  $-H$  or  $-CH_3$ ;

25

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each Ar<sub>3</sub> cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Q<sub>1</sub> is independently selected from the group consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -N(R<sub>9</sub>)(R<sub>10</sub>), and



wherein each R<sub>9</sub> and R<sub>10</sub> are independently a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub> wherein Ar<sub>3</sub> is phenyl;

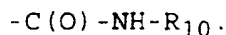
provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub> group which comprises one or more additional -Ar<sub>3</sub> groups, said additional -Ar<sub>3</sub> groups are not substituted with another -Ar<sub>3</sub>.

Other more preferred compounds of embodiment E, employ formula (II) wherein R<sub>1</sub> is (e10), X<sub>5</sub> is N, R<sub>3</sub> is -CO-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>, R<sub>11</sub> is -Ar<sub>4</sub>, and the other substituents are as defined above.

More preferably, in these more preferred compounds, R<sub>5</sub> is selected from the group consisting of:

-C(O)-R<sub>10</sub>,  
-C(O)O-R<sub>9</sub>, and

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Alternatively, in these more preferred compounds,  $R_5$  is selected from the group consisting of:

- 5            $-S(O)_2-R_9$ ,  
           $-S(O)_2-NH-R_{10}$ ,  
           $-C(O)-C(O)-R_{10}$ ,  
           $-R_9$ , and  
           $-C(O)-C(O)-OR_{10}$ .

Most preferably, in these more preferred compounds

10            $m$  is 1;

$T_1$  is O or S;

15            $R_{15}$  is  $-OH$  or  $-OC_{1-4}$  straight or branched alkyl group optionally substituted with  $-Ar_3$ ,  $-OH$ ,  $-OR_9$ , or  $-CO_2H$ , wherein the  $R_9$  is a  $-C_{1-4}$  branched or straight alkyl group, wherein  $Ar_3$  is morpholinyl or phenyl, wherein the phenyl is optionally substituted with  $Q_1$ ;

$R_{21}$  is  $-H$  or  $-CH_3$ ;

20           each  $Ar_3$  cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl,  
25           benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

30           each  $Ar_4$  cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, or thienyl.

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said cyclic group being singly or multiply substituted by  $-Q_1$ ;

each  $Q_1$  is independently selected from the group consisting of  $-NH_2$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-OH$ ,  $-R_9$ ,  $-NH-R_5$  wherein  $R_5$  is  $-C(O)-R_{10}$  or  $-S(O)_2-R_9$ ,  $-OR_5$  wherein  $R_5$  is  $-C(O)-R_{10}$ ,  $-OR_9$ ,  $-N(R_9)(R_{10})$ , and



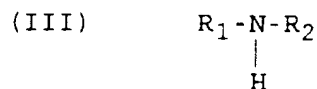
wherein each  $R_9$  and  $R_{10}$  are independently a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$  wherein  $Ar_3$  is phenyl;

15

provided that when  $-Ar_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-Ar_3$  groups, said additional  $-Ar_3$  groups are not substituted with another  $-Ar_3$ .

20

The ICE inhibitors of another embodiment (F) of this invention are those of formula (III):

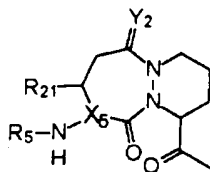


25 wherein:

$R_1$  is selected from the group consisting of the following formulae:

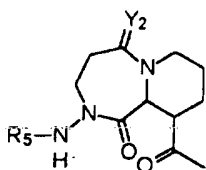
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(e10)



;

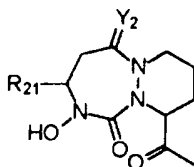
(e11)



;

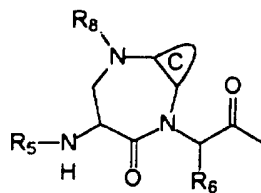
5

(e12)



;

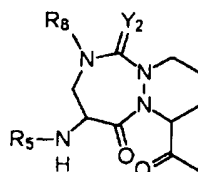
(w2)



;

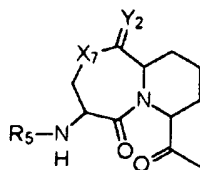
10

(y1)



;

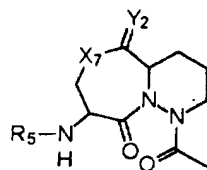
(y2)



;

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(z)

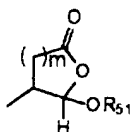


; and

ring C is chosen from the group consisting of  
benzo, pyrido, thieno, pyrrolo, furano, thiazolo,  
5 isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo,  
cyclopentyl, and cyclohexyl;

R<sub>2</sub> is:

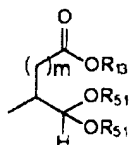
(a)



, or

10

(b)



;

m is 1 or 2;

each R<sub>5</sub> is independently selected from  
the group consisting of:

15

- C(O)-R<sub>10</sub>,
- C(O)O-R<sub>9</sub>,
- C(O)-N(R<sub>10</sub>)(R<sub>10</sub>)
- S(O)<sub>2</sub>-R<sub>9</sub>,
- S(O)<sub>2</sub>-NH-R<sub>10</sub>,
- C(O)-CH<sub>2</sub>-O-R<sub>9</sub>,
- 20 -C(O)C(O)-R<sub>10</sub>,
- R<sub>9</sub>,
- H,



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-C(O)C(O)-OR<sub>10</sub>, and  
-C(O)C(O)-N(R<sub>9</sub>)(R<sub>10</sub>);

X<sub>5</sub> is CH or N;

5

Y<sub>2</sub> is H<sub>2</sub> or O;

X<sub>7</sub> is -N(R<sub>8</sub>)- or -O-;

10 R<sub>6</sub> is selected from the group consisting of -H and  
-CH<sub>3</sub>;

R<sub>8</sub> is selected from the group consisting of:

15 -C(O)-R<sub>10</sub>,  
-C(O)O-R<sub>9</sub>,  
-C(O)-N(H)-R<sub>10</sub>,  
-S(O)<sub>2</sub>-R<sub>9</sub>,  
-S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
-C(O)-CH<sub>2</sub>-OR<sub>10</sub>,  
-C(O)C(O)-R<sub>10</sub>;  
20 -C(O)-CH<sub>2</sub>N(R<sub>10</sub>)(R<sub>10</sub>),  
-C(O)-CH<sub>2</sub>C(O)-O-R<sub>9</sub>,  
-C(O)-CH<sub>2</sub>C(O)-R<sub>9</sub>,  
-H, and  
-C(O)-C(O)-OR<sub>10</sub>;

25 each R<sub>9</sub> is independently selected from the group  
consisting of -Ar<sub>3</sub> and a -C<sub>1-6</sub> straight or branched  
alkyl group optionally substituted with Ar<sub>3</sub>, wherein  
the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

30 each R<sub>10</sub> is independently selected from the group  
consisting of -H, -Ar<sub>3</sub>, a C<sub>3-6</sub> cycloalkyl group, and a  
-C<sub>1-6</sub> straight or branched alkyl group optionally  
substituted with Ar<sub>3</sub>, wherein the -C<sub>1-6</sub> alkyl group is

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optionally unsaturated;

$R_{13}$  is selected from the group consisting of H,  $Ar_3$ , and a  $C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$ ,  $-CONH_2$ ,  $-OR_5$ ,  $-OH$ ,  
 5  $-OR_9$ , or  $-CO_2H$ ;

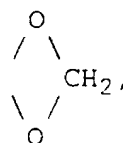
each  $R_{21}$  is independently selected from the group consisting of  $-H$  or a  $-C_{1-6}$  straight or branched alkyl group;

each  $R_{51}$  is independently selected from the group  
 10 consisting of  $R_9$ ,  $-C(O)-R_9$ ,  $-C(O)-N(H)-R_9$ , or each  $R_{51}$  taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing  $-O-$ ,  $-S-$ , or  $-NH-$ ;

each  $Ar_3$  is a cyclic group independently selected from the set consisting of an aryl group which contains  
 15 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from  $-O-$ ,  $-S-$ ,  $-SO-$ ,  $SO_2$ ,  $=N-$ , and  $-NH-$ ,  
 20 said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

25 each  $Q_1$  is independently selected from the group consisting of  $-NH_2$ ,  $-CO_2H$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-I$ ,  $-NO_2$ ,  $-CN$ ,  $=O$ ,  $-OH$ ,  $-perfluoro\ C_{1-3}\ alkyl$ ,  $R_5$ ,  $-OR_5$ ,  $-NHR_5$ ,  $OR_9$ ,  $-N(R_9)(R_{10})$ ,  $R_9$ ,  $-C(O)-R_{10}$ , and

30



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provided that when  $-\text{Ar}_3$  is substituted with a  $\text{Q}_1$  group which comprises one or more additional  $-\text{Ar}_3$  groups, said additional  $-\text{Ar}_3$  groups are not substituted with another  $-\text{Ar}_3$ .

Preferred compounds of embodiment F employ formula (III), wherein  $\text{R}_1$  is (w2) and the other substituents are as defined above.

Preferably, when  $\text{R}_1$  is (w2):

$m$  is 1;

ring C is benzo, pyrido, or thieno;

$\text{R}_5$  is selected from the group consisting of:

- C(O)- $\text{R}_{10}$ , wherein  $\text{R}_{10}$  is  $-\text{Ar}_3$ ;
- C(O)O- $\text{R}_9$ , wherein  $\text{R}_9$  is  $-\text{CH}_2-\text{Ar}_3$ ;
- C(O)C(O)- $\text{R}_{10}$ , wherein  $\text{R}_{10}$  is  $-\text{Ar}_3$ ;
- $\text{R}_9$ , wherein  $\text{R}_9$  is a  $\text{C}_{1-2}$  alkyl group substituted with  $-\text{Ar}_3$ ; and
- C(O)C(O)-O $\text{R}_{10}$ , wherein  $\text{R}_{10}$  is  $-\text{CH}_2\text{Ar}_3$ ;

$\text{R}_6$  is H;

$\text{R}_8$  is selected from the group consisting  $-\text{C(O)}-\text{R}_{10}$ ,  $-\text{C(O)}-\text{CH}_2-\text{OR}_{10}$ , and  $-\text{C(O)}\text{CH}_2-\text{N}(\text{R}_{10})(\text{R}_{10})$ , wherein  $\text{R}_{10}$  is H,  $\text{CH}_3$ , or  $-\text{CH}_2\text{CH}_3$ ;

$\text{R}_{13}$  is H or a  $\text{C}_{1-4}$  straight or branched alkyl group optionally substituted with  $\text{Ar}_3$ ,  $-\text{OH}$ ,  $-\text{OR}_9$ ,  $-\text{CO}_2\text{H}$ , wherein the  $\text{R}_9$  is a  $\text{C}_{1-4}$  branched or straight chain alkyl group; wherein  $\text{Ar}_3$  is morpholinyl or phenyl, wherein the phenyl is optionally substituted with  $\text{Q}_1$ ;

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Ar<sub>3</sub> is phenyl, naphthyl, thienyl, quinolinyl,  
 isoquinolinyl, thiazolyl, benzimidazolyl,  
 thienothienyl, thiadiazolyl, benzotriazolyl,  
 5 benzo[b]thiophenyl, benzofuranyl, and indolyl;

each Q<sub>1</sub> is independently selected from the group  
 consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub>  
 wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is  
 -C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -NHR<sub>9</sub>, and



15 wherein each R<sub>9</sub> and R<sub>10</sub> are independently a -C<sub>1-6</sub>  
 straight or branched alkyl group optionally substituted  
 with Ar<sub>3</sub> wherein Ar<sub>3</sub> is phenyl;

provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub>  
 20 group which comprises one or more additional -Ar<sub>3</sub>  
 groups, said additional -Ar<sub>3</sub> groups are not substituted  
 with another -Ar<sub>3</sub>.

Other preferred compounds of embodiment F employ  
 formula (III), wherein R<sub>1</sub> is (e11) and the other  
 25 substituents are as defined above.

Other preferred compounds of embodiment F employ  
 formula (III), wherein R<sub>1</sub> is (e12) and the other  
 substituents are as defined above.

Other preferred compounds of embodiment F employ  
 30 formula (III), wherein R<sub>1</sub> is (y1) and the other  
 substituents are as defined above.

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Other preferred compounds of embodiment F employ formula (III), wherein  $R_1$  is (y2) and the other substituents are as defined above.

5 Other preferred compounds of embodiment F employ formula (III), wherein  $R_1$  is (z) and the other substituents are as defined above.

10 Other preferred compounds of embodiment F employ formula (III), wherein  $R_1$  is (e10) and  $X_5$  is CH (also referred to herein as e10-B), and the other substituents are as defined above.

Other preferred compounds of embodiment F employ formula (III), wherein  $R_1$  is (e10) and  $X_5$  is N, (also referred to herein as e10-A) and the other substituents are as defined above.

15 Preferably, when  $R_1$  is (e11), (e12), (y1), (y2), (z), (e10-A), and (e10-B),  $R_5$  is selected from the group consisting of:

20 -C(O)- $R_{10}$ ,  
-C(O)O- $R_9$ , and  
-C(O)-NH- $R_{10}$ .

Alternatively, when  $R_1$  is (e11), (e12), (y1), (y2), (z), (e10-A), and (e10-B),  $R_5$  is selected from the group consisting of:

25 -S(O)<sub>2</sub>- $R_9$ ,  
-S(O)<sub>2</sub>-NH- $R_{10}$ ,  
-C(O)-C(O)- $R_{10}$ ,  
- $R_9$ ,  
-C(O)-C(O)-OR<sub>10</sub>, and  
-C(O)C(O)-N( $R_9$ )( $R_{10}$ ).

30 More preferably,  $R_5$  is R-C(O)-C(O)- $R_{10}$ .

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Alternatively,  $R_5$  is  $-C(O)-C(O)-OR_{10}$ .

More preferably when  $R_1$  is (e11), (e12), (y1), (y2), (z), (e10-A), and (e10-B):

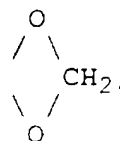
m is 1;

5  $R_{21}$  is -H or  $-CH_3$ ;

$R_{51}$  is a  $C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$ , wherein the  $Ar_3$  cyclic group is phenyl, said cyclic group optionally being multiply or singly substituted by  $-Q_1$ ;

10 each  $Ar_3$  cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl,  
15 benzo[b]thiophenyl, pyridyl, benzofuranyl, or indolyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

each  $Q_1$  is independently selected from the group consisting of  $-NH_2$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-OH$ ,  $-R_9$ ,  $-NH-R_5$   
20 wherein  $R_5$  is  $-C(O)-R_{10}$  or  $-S(O)_2-R_9$ ,  $-OR_5$  wherein  $R_5$  is  $-C(O)-R_{10}$ ,  $-OR_9$ ,  $-N(R_9)(R_{10})$ , and



25

wherein each  $R_9$  and  $R_{10}$  are independently a  $-C_{1-6}$  straight or branched alkyl group optionally substituted  
30 with  $Ar_3$ , wherein the  $Ar_3$  cyclic group is phenyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

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provided that when  $-Ar_3$  is substituted with a  $-Q_1$  group which comprises one or more additional  $-Ar_3$  groups, said additional  $-Ar_3$  groups are not substituted  
5 with another  $-Ar_3$ .

More preferably, in these more preferred compounds, the  $Ar_3$  cyclic group is selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl,  
10 isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ .

15 Compounds in a preferred form of this embodiment F are those wherein:

$R_5$  is  $-C(O)-R_{10}$ , wherein:

$R_{10}$  is  $Ar_3$ , wherein the  $Ar_3$  cyclic group is phenyl, said cyclic group optionally being singly or multiply  
20 substituted by:

$-F$ ,

$-Cl$ ,

$-N(H)-R_5$ , wherein  $-R_5$  is  $-H$  or  $-C(O)-R_{10}$ , wherein  $R_{10}$  is a  $-C_{1-6}$  straight or branched alkyl group  
25 optionally substituted with  $Ar_3$ , wherein the  $Ar_3$  cyclic group is phenyl, said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ,

$-N(R_9)(R_{10})$ , wherein  $R_9$  and  $R_{10}$  are independently a  $-C_{1-4}$  straight or branched alkyl group, or

30  $-O-R_5$ , wherein  $R_5$  is  $H$  or a  $-C_{1-4}$  straight or branched alkyl group.

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More preferably the Ar<sub>3</sub> cyclic group is phenyl optionally being singly or multiply substituted at the 3- or 5-position by -Cl or at the 4-position by -NH-R<sub>5</sub>, -N(R<sub>9</sub>)(R<sub>10</sub>), or -O-R<sub>5</sub>.

5 Other preferred compounds of embodiment F include those wherein R<sub>5</sub> is -C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is Ar<sub>3</sub> and the Ar<sub>3</sub> cyclic group is selected from the group consisting of indolyl, benzimidazolyl, thienyl, and benzo[b]thiophenyl, and said cyclic group optionally  
10 being singly or multiply substituted by -Q<sub>1</sub>;

Other preferred compounds of embodiment F include those wherein R<sub>5</sub> is -C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is Ar<sub>3</sub> and the Ar<sub>3</sub> cyclic group is selected from quinolyl and isoquinolyl, and said cyclic group optionally being  
15 singly or multiply substituted by -Q<sub>1</sub>.

Other preferred compounds of embodiment F are those wherein R<sub>5</sub> is -C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is Ar<sub>3</sub>; wherein the Ar<sub>3</sub> cyclic group is phenyl, substituted by



25 In another form of embodiment F the compounds are as described above, further provided that when:

m is 1;  
R<sub>1</sub> is (e10);  
X<sub>5</sub> is CH;  
R<sub>15</sub> is -OH;  
30 R<sub>21</sub> is -H; and



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$Y_2$  is O and  $R_3$  is  $-C(O)-H$ , then  $R_5$  cannot be:

$-C(O)-R_{10}$ , wherein  $R_{10}$  is  $-Ar_3$  and the  $Ar_3$  cyclic group is phenyl, unsubstituted by  $-Q_1$ , 4-

(carboxymethoxy)phenyl, 2-fluorophenyl, 2-pyridyl, N-  
5 (4-methylpiperazino)methylphenyl, or

$-C(O)-OR_9$ , wherein  $R_9$  is  $-CH_2-Ar_3$ , and the  $Ar_3$  cyclic group is phenyl, unsubstituted by  $-Q_1$ ; and when

$Y_2$  is O,  $R_3$  is  $-C(O)-CH_2-T_1-R_{11}$ ,  $T_1$  is O, and  $R_{11}$  is  $Ar_4$ , wherein the  $Ar_4$  cyclic group is 5-(1-(4-chlorophenyl)-3-trifluoromethyl)pyrazolyl), then  $R_5$   
10 cannot be:

$-C(O)-R_{10}$ , wherein  $R_{10}$  is  $-Ar_3$  and the  $Ar_3$  cyclic group is 4-(dimethylaminomethyl)phenyl, phenyl, 4-(carboxymethylthio)phenyl, 4-(carboxyethylthio)phenyl,  
15 4-(carboxyethyl)phenyl, 4-(carboxypropyl)phenyl, 2-fluorophenyl, 2-pyridyl, N-(4-methylpiperazino)methylphenyl, or

$-C(O)-OR_9$ , wherein  $R_9$  is  $-CH_2-Ar_3$  and the  $Ar_3$  cyclic group is phenyl;

20 and when  $R_{11}$  is  $Ar_4$ , wherein the  $Ar_4$  cyclic group is 5-(1-phenyl-3-trifluoromethyl)pyrazolyl), then  $R_5$  cannot be:

$-C(O)-OR_9$ , wherein  $R_9$  is  $-CH_2-Ar_3$ , and the  $Ar_3$  cyclic group is phenyl;

25 and when  $R_{11}$  is  $Ar_4$ , wherein the  $Ar_4$  cyclic group is 5-(1-(2-pyridyl)-3-trifluoromethyl)pyrazolyl), then  $R_5$  cannot be:

$-C(O)-R_{10}$ , wherein  $R_{10}$  is  $-Ar_3$  and the  $Ar_3$  cyclic group is 4-(dimethylaminomethyl)phenyl, or

30  $-C(O)-OR_9$ , wherein  $R_9$  is  $-CH_2-Ar_3$ , and the  $Ar_3$  cyclic group is phenyl, unsubstituted by  $-Q_1$ ; and when

$Y_2$  is O,  $R_3$  is  $-C(O)-CH_2-T_1-R_{11}$ ,  $T_1$  is O, and  $R_{11}$  is  $-C(O)-Ar_4$ , wherein the  $Ar_4$  cyclic group is 2,5-

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dichlorophenyl, then  $R_5$  cannot be:

-C(O)- $R_{10}$ , wherein  $R_{10}$  is - $Ar_3$  and the  $Ar_3$  cyclic group is 4-(dimethylaminomethyl)phenyl, 4-(N-morpholinomethyl)phenyl, 4-(N-methylpiperazino)methyl)phenyl, 4-(N-(2-methyl)imidazolylmethyl)phenyl, 5-benzimidazolyl, 5-benztriazolyl, N-carboethoxy-5-benztriazolyl, N-carboethoxy-5-benzimidazolyl, or

-C(O)- $OR_9$ , wherein  $R_9$  is - $CH_2-Ar_3$ , and the  $Ar_3$  cyclic group is phenyl, unsubstituted by - $Q_1$ ,; and when

$Y_2$  is  $H_2$ ,  $R_3$  is -C(O)- $CH_2-T_1-R_{11}$ ,  $T_1$  is O, and  $R_{11}$  is

-C(O)- $Ar_4$ , wherein the  $Ar_4$  cyclic group is 2,5-dichlorophenyl, then  $R_5$  cannot be:

-C(O)- $OR_9$ , wherein  $R_9$  is - $CH_2-Ar_3$  and the  $Ar_3$  cyclic group is phenyl.

In another form of embodiment F, preferred compounds are those wherein  $R_{21}$  is -H.

Alternatively, preferred compounds are those wherein  $R_{21}$  is - $CH_3$ .

Preferred compounds of embodiment F employ formula (III), wherein  $R_1$  is (w2) and the other substituents are as defined above.

More preferably,  $R_1$  is (w2) and

m is 1;

ring C is benzo, pyrido, or thieno;

$R_3$  is selected from the group consisting of -C(O)-H, -C(O)- $Ar_2$ , and -C(O) $CH_2-T_1-R_{11}$ ;

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R<sub>5</sub> is selected from the group consisting of:

- C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is -Ar<sub>3</sub>;
- C(O)O-R<sub>9</sub>, wherein R<sub>9</sub> is -CH<sub>2</sub>-Ar<sub>3</sub>;
- C(O)C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is -Ar<sub>3</sub>;
- 5        -R<sub>9</sub>, wherein R<sub>9</sub> is a C<sub>1-2</sub> alkyl group  
substituted with -Ar<sub>3</sub>; and
- C(O)C(O)-OR<sub>10</sub>, wherein R<sub>10</sub> is -CH<sub>2</sub>Ar<sub>3</sub>;

T<sub>1</sub> is O or S;

10        R<sub>6</sub> is H;

R<sub>8</sub> is selected from the group consisting -C(O)-R<sub>10</sub>,  
-C(O)-CH<sub>2</sub>-OR<sub>10</sub>, and -C(O)CH<sub>2</sub>-N(R<sub>10</sub>)(R<sub>10</sub>), wherein R<sub>10</sub> is  
H, CH<sub>3</sub>, or -CH<sub>2</sub>CH<sub>3</sub>;

15        R<sub>11</sub> is selected from the group consisting of -Ar<sub>4</sub>,  
-(CH<sub>2</sub>)<sub>1-3</sub>-Ar<sub>4</sub>, and -C(O)-Ar<sub>4</sub>;

R<sub>15</sub> is -OH or -OC<sub>1-4</sub> straight or branched alkyl  
group optionally substituted with -Ar<sub>3</sub>, -OH, -OR<sub>9</sub>, or  
-CO<sub>2</sub>H, wherein the R<sub>9</sub> is a -C<sub>1-4</sub> branched or straight  
alkyl group, wherein Ar<sub>3</sub> is morpholinyl or phenyl,  
20        wherein the phenyl is optionally substituted with Q<sub>1</sub>;

Ar<sub>2</sub> is (hh);

Y is O;

25        each Ar<sub>3</sub> cyclic group is independently selected  
from the set consisting of phenyl, naphthyl, thienyl,  
quinolinyl, isoquinolinyl, thiazolyl, benzimidazolyl,  
thienothienyl, thiadiazolyl, benzotriazolyl,  
benzo[b]thiophenyl, benzofuranyl, and indolyl, and said  
cyclic group optionally being singly or multiply  
30        substituted by -Q<sub>1</sub>;

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each Ar<sub>4</sub> cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, naphthyl, pyridinyl, oxazolyl, pyrimidinyl, or indolyl, said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Q<sub>1</sub> is independently selected from the group consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -N(R<sub>9</sub>)(R<sub>10</sub>), and



15 wherein each R<sub>9</sub> and R<sub>10</sub> are independently a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub> wherein Ar<sub>3</sub> is phenyl;

20 provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub> group which comprises one or more additional -Ar<sub>3</sub> groups, said additional -Ar<sub>3</sub> groups are not substituted with another -Ar<sub>3</sub>.

Other preferred compounds of embodiment F employ formula (III), wherein R<sub>1</sub> is (e11) and the other substituents are as defined above.

Other preferred compounds of embodiment F employ formula (III), wherein R<sub>1</sub> is (e12) and the other substituents are as defined above.

30 Other preferred compounds of embodiment F employ formula (III) wherein R<sub>1</sub> is (y1) and the other substituents are as defined above.

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Other preferred compounds of embodiment F employ formula (III) wherein  $R_1$  is (y2) and the other substituents are as defined above.

5 Other preferred compounds of embodiment F of employ formula (III) wherein  $R_1$  is (z) and the other substituents are as defined above.

Other preferred compounds of embodiment F employ formula (III) wherein  $R_1$  is (e10),  $X_5$  is CH, and the other substituents are as defined above.

10 Other preferred compounds of embodiment F employ formula (III) wherein  $R_1$  is (e10),  $X_5$  is N, and the other substituents are as defined above.

More preferably, in these more preferred compounds,  $R_5$  is selected from the group consisting of:

15        -C(O)- $R_{10}$ ,  
         -C(O)O- $R_9$ , and  
         -C(O)-NH- $R_{10}$ .

Alternatively, in these more preferred compounds,  $R_5$  is selected from the group consisting of:

20        -S(O)<sub>2</sub>- $R_9$ ,  
         -S(O)<sub>2</sub>-NH- $R_{10}$ ,  
         -C(O)-C(O)- $R_{10}$ ,  
         - $R_9$ ,  
         -C(O)-C(O)-OR<sub>10</sub>, and  
25        -C(O)C(O)-N( $R_9$ ) ( $R_{10}$ ).

Most preferably, in these more preferred compounds,

m is 1;

$R_{13}$  is H or a -C<sub>1-4</sub> straight or branched alkyl

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group optionally substituted with  $-\text{Ar}_3$ ,  $-\text{OH}$ ,  $-\text{OR}_9$ , or  $-\text{CO}_2\text{H}$ , wherein the  $\text{R}_9$  is a  $-\text{C}_{1-4}$  branched or straight alkyl group, wherein  $\text{Ar}_3$  is morpholinyl or phenyl, wherein the phenyl is optionally substituted with  $\text{Q}_1$ ;

5  $\text{R}_{21}$  is  $-\text{H}$  or  $-\text{CH}_3$ ;

$\text{R}_{51}$  is a  $\text{C}_{1-6}$  straight or branched alkyl group optionally substituted with  $\text{Ar}_3$ , wherein  $\text{Ar}_3$  is phenyl, optionally substituted by  $-\text{Q}_1$ ;

10 each  $\text{Ar}_3$  cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, 15 benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by  $-\text{Q}_1$ ;

each  $\text{Q}_1$  is independently selected from the group consisting of  $-\text{NH}_2$ ,  $-\text{Cl}$ ,  $-\text{F}$ ,  $-\text{Br}$ ,  $-\text{OH}$ ,  $-\text{R}_9$ ,  $-\text{NH}-\text{R}_5$  20 wherein  $\text{R}_5$  is  $-\text{C}(\text{O})-\text{R}_{10}$  or  $-\text{S}(\text{O})_2-\text{R}_9$ ,  $-\text{OR}_5$  wherein  $\text{R}_5$  is  $-\text{C}(\text{O})-\text{R}_{10}$ ,  $-\text{OR}_9$ ,  $-\text{N}(\text{R}_9)(\text{R}_{10})$ , and



wherein each  $\text{R}_9$  and  $\text{R}_{10}$  are independently a  $-\text{C}_{1-6}$  straight or branched alkyl group optionally substituted with  $\text{Ar}_3$  wherein  $\text{Ar}_3$  is phenyl;

30

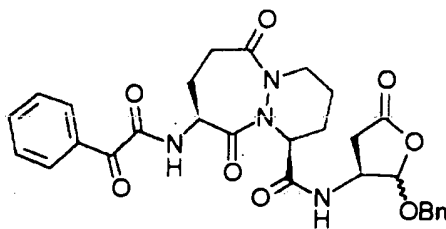
provided that when  $-\text{Ar}_3$  is substituted with a  $\text{Q}_1$  group which comprises one or more additional  $-\text{Ar}_3$  groups, said additional  $-\text{Ar}_3$  groups are not substituted

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with another -Ar<sub>3</sub>.

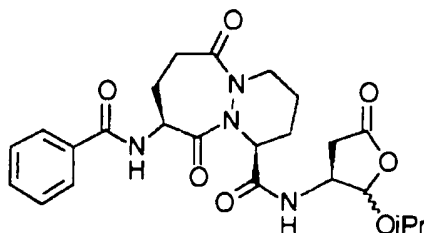
Preferred compounds of embodiment (F) include, but are not limited to:

2001

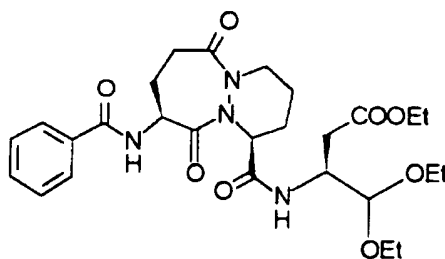


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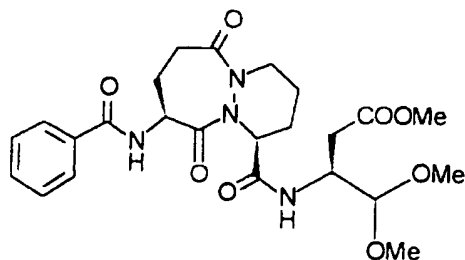
2100a



2100b

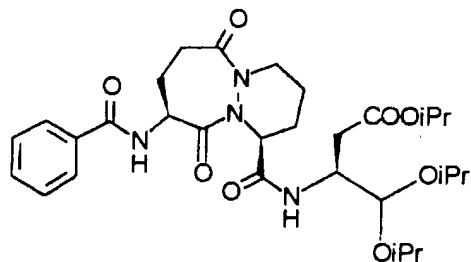


2100c

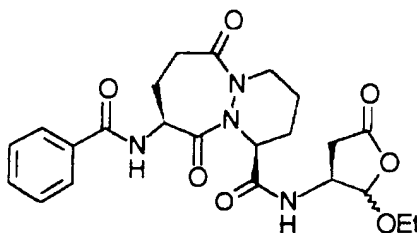


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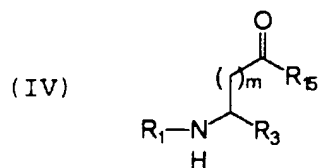
2100d



2100e



The ICE inhibitors of another embodiment (G)  
 5 of this invention are those of formula (IV):



wherein:

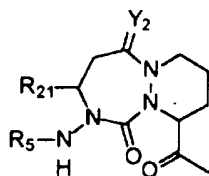
$m$  is 1 or 2;

10  $R_1$  is selected from the group consisting of the  
 following formulae:



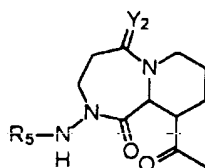
- 171 -

(e10-A)



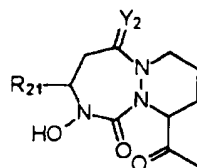
;

(e11)



;

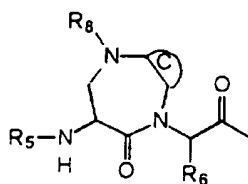
(e12)



;

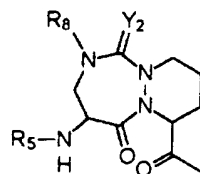
5

(w2)



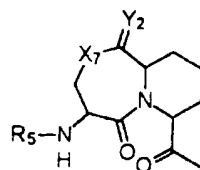
;

(y1)



;

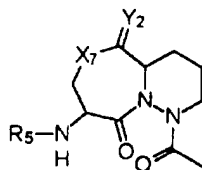
(y2)



;

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(z)



; and

ring C is chosen from the group consisting of  
benzo, pyrido, thieno, pyrrolo, furano, thiazolo,  
5 isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo,  
cyclopentyl, and cyclohexyl;

R<sub>3</sub> is selected from the group consisting of:

- CN,
- C(O)-H,
- 10 -C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>,
- C(O)-CH<sub>2</sub>-F,
- C=N-O-R<sub>9</sub>, and
- CO-Ar<sub>2</sub>;

each R<sub>5</sub> is independently selected from the  
15 group consisting of:

- C(O)-R<sub>10</sub>,
- C(O)O-R<sub>9</sub>,
- C(O)-N(R<sub>10</sub>)(R<sub>10</sub>)
- S(O)<sub>2</sub>-R<sub>9</sub>,
- 20 -S(O)<sub>2</sub>-NH-R<sub>10</sub>,
- C(O)-CH<sub>2</sub>-O-R<sub>9</sub>,
- C(O)C(O)-R<sub>10</sub>,
- R<sub>9</sub>,
- H,
- 25 -C(O)C(O)-OR<sub>10</sub>, and
- C(O)C(O)-N(R<sub>9</sub>)(R<sub>10</sub>);

Y<sub>2</sub> is H<sub>2</sub> or O;

X<sub>7</sub> is -N(R<sub>8</sub>)- or -O-;

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each  $T_1$  is independently selected from the group consisting of -O-, -S-, -S(O)-, and -S(O)<sub>2</sub>-;

5  $R_6$  is selected from the group consisting of -H and -CH<sub>3</sub>;

$R_8$  is selected from the group consisting of:

10 -C(O)-R<sub>10</sub>,  
-C(O)O-R<sub>9</sub>,  
-C(O)-NH-R<sub>10</sub>,  
-S(O)<sub>2</sub>-R<sub>9</sub>,  
-S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
-C(O)-CH<sub>2</sub>-OR<sub>10</sub>,  
-C(O)C(O)-R<sub>10</sub>,  
15 -C(O)-CH<sub>2</sub>-N(R<sub>10</sub>)(R<sub>10</sub>),  
-C(O)-CH<sub>2</sub>C(O)-O-R<sub>9</sub>,  
-C(O)-CH<sub>2</sub>C(O)-R<sub>9</sub>,  
-H, and  
-C(O)-C(O)-OR<sub>10</sub>;

20 each  $R_9$  is independently selected from the group consisting of -Ar<sub>3</sub> and a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, wherein the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

25 each  $R_{10}$  is independently selected from the group consisting of -H, -Ar<sub>3</sub>, a C<sub>3-6</sub> cycloalkyl group, and a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, wherein the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

30 each  $R_{11}$  is independently selected from the group consisting of:

-Ar<sub>4</sub>,  
-(CH<sub>2</sub>)<sub>1-3</sub>-Ar<sub>4</sub>,  
-H, and

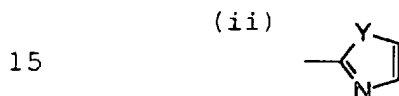
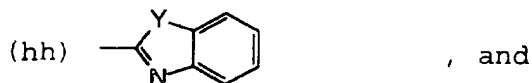
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-C(O)-Ar<sub>4</sub>;

R<sub>15</sub> is selected from the group consisting of -OH, -OAr<sub>3</sub>, -N(H)-OH, and -OC<sub>1-6</sub>, wherein C<sub>1-6</sub> is a straight or branched alkyl group optionally substituted with  
 5 Ar<sub>3</sub>, -CONH<sub>2</sub>, -OR<sub>5</sub>, -OH, -OR<sub>9</sub>, or -CO<sub>2</sub>H;

each R<sub>21</sub> is independently selected from the group consisting of -H or a -C<sub>1-6</sub> straight or branched alkyl group;

Ar<sub>2</sub> is independently selected from the following  
 10 group, in which any ring may optionally be singly or multiply substituted by -Q<sub>1</sub> or phenyl, optionally substituted by Q<sub>1</sub>:



wherein each Y is independently selected from the group consisting of O and S;

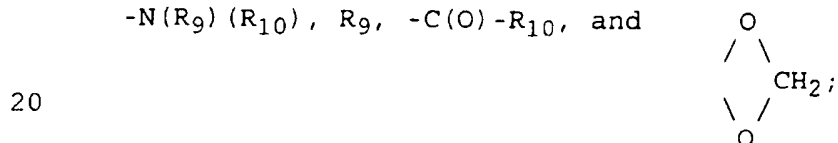
each Ar<sub>3</sub> is a cyclic group independently selected from the set consisting of an aryl group which contains  
 20 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, and -NH-,  
 25 -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or

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multiply substituted by  $-Q_1$ ;

each  $Ar_4$  is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from  $-O-$ ,  $-S-$ ,  $-SO-$ ,  $SO_2$ ,  $=N-$ ,  $-NH-$ ,  $-N(R_5)-$ , and  $-N(R_9)-$  said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

each  $Q_1$  is independently selected from the group consisting of  $-NH_2$ ,  $-CO_2H$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-I$ ,  $-NO_2$ ,  $-CN$ ,  $=O$ ,  $-OH$ ,  $-perfluoro\ C_{1-3}\ alkyl$ ,  $R_5$ ,  $-OR_5$ ,  $-NHR_5$ ,  $OR_9$ ,  $-N(R_9)(R_{10})$ ,  $R_9$ ,  $-C(O)-R_{10}$ , and



provided that when  $-Ar_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-Ar_3$  groups, said additional  $-Ar_3$  groups are not substituted with another  $-Ar_3$ ;

Preferred compounds of embodiment G employ formula (IV), wherein  $R_1$  is (w2) and the other substituents are as defined above.

Preferably, when  $R_1$  is (w2):

m is 1;

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ring C is benzo, pyrido, or thieno;

R<sub>5</sub> is selected from the group consisting of:

- C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is -Ar<sub>3</sub>;
- C(O)O-R<sub>9</sub>, wherein R<sub>9</sub> is -CH<sub>2</sub>-Ar<sub>3</sub>;
- 5       -C(O)C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is -Ar<sub>3</sub>;
- R<sub>9</sub>, wherein R<sub>9</sub> is a C<sub>1-2</sub> alkyl group substituted with -Ar<sub>3</sub>; and
- C(O)C(O)-OR<sub>10</sub>, wherein R<sub>10</sub> is -CH<sub>2</sub>Ar<sub>3</sub>;

10       R<sub>6</sub> is H;

R<sub>8</sub> is selected from the group consisting -C(O)-R<sub>10</sub>, -C(O)-CH<sub>2</sub>-OR<sub>10</sub>, and -C(O)CH<sub>2</sub>-N(R<sub>10</sub>)(R<sub>10</sub>), wherein R<sub>10</sub> is H, CH<sub>3</sub>, or -CH<sub>2</sub>CH<sub>3</sub>;

15       R<sub>13</sub> is H or a C<sub>1-4</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, -OH, -OR<sub>9</sub>, -CO<sub>2</sub>H, wherein the R<sub>9</sub> is a C<sub>1-4</sub> branched or straight chain alkyl group; wherein Ar<sub>3</sub> is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q<sub>1</sub>;

20       Ar<sub>3</sub> is phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, thiazolyl, benzimidazolyl, thienothienyl, thiadiazolyl, benzotriazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl;

25       each Q<sub>1</sub> is independently selected from the group consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -NHR<sub>9</sub>, and



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wherein each  $R_9$  and  $R_{10}$  are independently a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$  wherein  $Ar_3$  is phenyl;

5           provided that when  $-Ar_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-Ar_3$  groups, said additional  $-Ar_3$  groups are not substituted with another  $-Ar_3$ .

10           Other preferred compounds of embodiment G employ formula (IV) wherein  $R_1$  is (e10-A) and the other substituents are as defined above.

Other preferred compounds of embodiment G employ formula (IV) wherein  $R_1$  is (e11) and the other substituents are as defined above.

15           Other preferred compounds of embodiment G employ formula (IV) wherein  $R_1$  is (e12) and the other substituents are as defined above.

20           Other preferred compounds of embodiment G employ formula (IV) wherein  $R_1$  is (y1) and the other substituents are as defined above.

Other preferred compounds of embodiment G employ formula (IV) wherein  $R_1$  is (y2) and the other substituents are as defined above.

25           Other preferred compounds of embodiment G employ formula (IV) wherein  $R_1$  is (z) and the other substituents are as defined above.

More preferred compounds of embodiment G are those wherein  $R_3$  is  $-CO-Ar_2$ .

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Most preferably, when  $R_3$  is  $-\text{CO}-\text{Ar}_2$ ,  $Y$  is  $\text{O}$ .

Other more preferred compounds are those wherein  $R_3$  is  $-\text{C}(\text{O})-\text{CH}_2-\text{T}_1-\text{R}_{11}$  and  $\text{R}_{11}$  is  $-(\text{CH}_2)_{1-3}-\text{Ar}_4$ .

Most preferably, when  $R_3$  is  $-\text{C}(\text{O})-\text{CH}_2-\text{T}_1-\text{R}_{11}$   
5 and  $\text{R}_{11}$  is  $-(\text{CH}_2)_{1-3}-\text{Ar}_4$ ,  $\text{T}_1$  is  $\text{O}$ .

Other more preferred compounds are those wherein:

$R_3$  is  $-\text{C}(\text{O})-\text{CH}_2-\text{T}_1-\text{R}_{11}$ ;

$\text{T}_1$  is  $\text{O}$ ; and

$\text{R}_{11}$  is  $-\text{C}(\text{O})-\text{Ar}_4$ .

10 Other more preferred compounds are those wherein  $R_3$  is  $-\text{C}(\text{O})-\text{H}$ .

Other more preferred compounds are those wherein  $R_3$  is  $-\text{CO}-\text{CH}_2-\text{T}_1-\text{R}_{11}$  and  $\text{R}_{11}$  is  $-\text{Ar}_4$ .

More preferably, when  $R_3$  is  $-\text{CO}-\text{CH}_2-\text{T}_1-\text{R}_{11}$  and  
15  $\text{R}_{11}$  is  $-\text{Ar}_4$ ,  $\text{T}_1$  is  $\text{O}$  or  $\text{S}$ .

More preferably, when  $\text{R}_1$  is  $(\text{e}11)$ ,  $(\text{e}12)$ ,  $(\text{y}1)$ ,  $(\text{y}2)$ ,  $(\text{z})$ ,  $(\text{e}10-\text{A})$ , and  $(\text{e}10-\text{B})$ ,  $\text{R}_5$  is selected from the group consisting of:

$-\text{C}(\text{O})-\text{R}_{10}$ ,

20  $-\text{C}(\text{O})\text{O}-\text{R}_9$ , and

$-\text{C}(\text{O})-\text{NH}-\text{R}_{10}$ .

Alternatively, when  $\text{R}_1$  is  $(\text{e}11)$ ,  $(\text{e}12)$ ,  $(\text{y}1)$ ,  $(\text{y}2)$ ,  $(\text{z})$ ,  $(\text{e}10-\text{A})$ , and  $(\text{e}10-\text{B})$ ,  $\text{R}_5$  is selected from the group consisting of:

25  $-\text{S}(\text{O})_2-\text{R}_9$ ,

$-\text{S}(\text{O})_2-\text{NH}-\text{R}_{10}$ ,

$-\text{C}(\text{O})-\text{C}(\text{O})-\text{R}_{10}$ ,

$-\text{R}_9$ ,



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-C(O)-C(O)-OR<sub>10</sub>, and  
 -C(O)-C(O)-N(R<sub>9</sub>)(R<sub>10</sub>).

More preferably, R<sub>5</sub> is -C(O)-C(O)-R<sub>10</sub>.

Alternatively, R<sub>5</sub> is -C(O)-C(O)-OR<sub>10</sub>.

5 Most preferably, when R<sub>1</sub> is (e11), (e12), (y1), (y2),  
 (z), (e10-A), and (e10-B),:

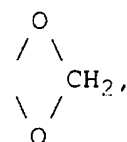
m is 1;

R<sub>21</sub> is -H or -CH<sub>3</sub>;

10 R<sub>51</sub> is a C<sub>1-6</sub> straight or branched alkyl group  
 optionally substituted with Ar<sub>3</sub>, wherein the Ar<sub>3</sub> cyclic  
 group is phenyl, said cyclic group optionally being  
 multiply or singly substituted by -Q<sub>1</sub>;

15 each Ar<sub>3</sub> cyclic group is independently selected  
 from the set consisting of phenyl, naphthyl, thienyl,  
 quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl,  
 isoxazolyl, benzotriazolyl, benzimidazolyl,  
 thienothienyl, imidazolyl, thiadiazolyl,  
 benzo[b]thiophenyl, pyridyl, benzofuranyl, or indolyl,  
 20 and said cyclic group optionally being singly or  
 multiply substituted by -Q<sub>1</sub>;

25 each Q<sub>1</sub> is independently selected from the group  
 consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub>  
 wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is  
 -C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -N(R<sub>9</sub>)(R<sub>10</sub>), and



30

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wherein each  $R_9$  and  $R_{10}$  are independently a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$ , wherein the  $Ar_3$  cyclic group is phenyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

provided that when  $-Ar_3$  is substituted with a  $-Q_1$  group which comprises one or more additional  $-Ar_3$  groups, said additional  $-Ar_3$  groups are not substituted with another  $-Ar_3$ .

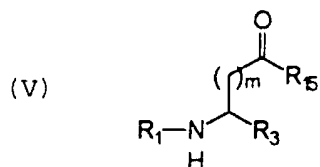
More preferably, in these more preferred compounds, the  $Ar_3$  cyclic group is selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ .

Compounds in a preferred form of embodiment G are those wherein  $R_{21}$  is H and the other substituents are as defined above.

Compounds in another preferred form of embodiment G are those wherein  $R_{21}$  is  $CH_3$  and the other substituents are as defined above.

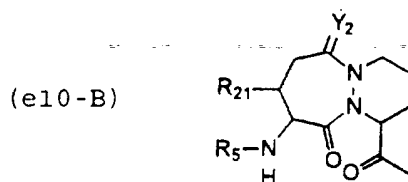
The ICE inhibitors of another embodiment (H) of this invention are those of formula (V):

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wherein:

m is 1 or 2;

5  $\text{R}_1$  is: $\text{R}_3$  is selected from the group consisting of:

- 10
- CN,
  - C(O)-H,
  - C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>,
  - C(O)-CH<sub>2</sub>-F,
  - C=N-O-R<sub>9</sub>, and
  - CO-Ar<sub>2</sub>;

15 each  $\text{R}_5$  is independently selected from the group consisting of:

- 20
- C(O)-R<sub>10</sub>,
  - C(O)O-R<sub>9</sub>,
  - C(O)-N(R<sub>10</sub>)(R<sub>10</sub>)
  - S(O)<sub>2</sub>-R<sub>9</sub>,
  - S(O)<sub>2</sub>-NH-R<sub>10</sub>,
  - C(O)-CH<sub>2</sub>-O-R<sub>9</sub>,
  - C(O)C(O)-R<sub>10</sub>,
  - R<sub>9</sub>,
  - H, and

25

  - C(O)C(O)-N(R<sub>9</sub>)(R<sub>10</sub>), and
  - C(O)C(O)-OR<sub>10</sub>;

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$Y_2$  is  $H_2$  or  $O$ ;

each  $T_1$  is independently selected from the group consisting of  $-O-$ ,  $-S-$ ,  $-S(O)-$ , and  $-S(O)_2-$ ;

5  $R_8$  is selected from the group consisting of:

- C(O)- $R_{10}$ ,
- C(O)O- $R_9$ ,
- C(O)-NH- $R_{10}$ ,
- S(O)<sub>2</sub>- $R_9$ ,
- 10 -S(O)<sub>2</sub>-NH- $R_{10}$ ,
- C(O)-CH<sub>2</sub>-OR<sub>10</sub>,
- C(O)C(O)- $R_{10}$ ,
- C(O)-CH<sub>2</sub>-N( $R_{10}$ )( $R_{10}$ ),
- C(O)-CH<sub>2</sub>C(O)-O- $R_9$ ,
- 15 -C(O)-CH<sub>2</sub>C(O)- $R_9$ ,
- H, and
- C(O)-C(O)-OR<sub>10</sub>;

each  $R_9$  is independently selected from the group consisting of  $-Ar_3$  and a  $-C_{1-6}$  straight or branched  
20 alkyl group optionally substituted with  $Ar_3$ , wherein the  $-C_{1-6}$  alkyl group is optionally unsaturated;

each  $R_{10}$  is independently selected from the group consisting of  $-H$ ,  $-Ar_3$ , a  $C_{3-6}$  cycloalkyl group, and a  
- $C_{1-6}$  straight or branched alkyl group optionally  
25 substituted with  $Ar_3$ , wherein the  $-C_{1-6}$  alkyl group is optionally unsaturated;

each  $R_{11}$  is independently selected from the group consisting of:

- $Ar_4$ ,
- 30 -(CH<sub>2</sub>)<sub>1-3</sub>- $Ar_4$ ,
- H, and
- C(O)- $Ar_4$ ;

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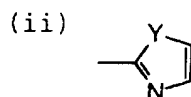
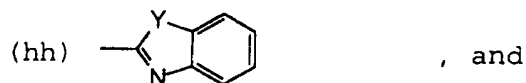
$R_{15}$  is selected from the group consisting of -OH, -OAr<sub>3</sub>, -N(H)-OH, and -OC<sub>1-6</sub>, wherein C<sub>1-6</sub> is a straight or branched alkyl group optionally substituted with Ar<sub>3</sub>,

5 -CONH<sub>2</sub>, -OR<sub>5</sub>, -OH, -OR<sub>9</sub>, or -CO<sub>2</sub>H;

$R_{21}$  is -CH<sub>3</sub>;

$Ar_2$  is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by -Q<sub>1</sub> or phenyl, optionally substituted by Q<sub>1</sub>:

10



wherein each Y is independently selected from the group consisting of O and S;

15

each Ar<sub>3</sub> is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, and -NH-, -N(R<sub>3</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

20

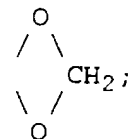
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each Ar<sub>4</sub> is a cyclic group independently selected

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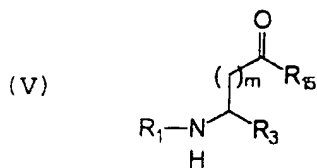
from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said  
 5 heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, -NH-, -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings,  
 10 and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Q<sub>1</sub> is independently selected from the group consisting of -NH<sub>2</sub>, -CO<sub>2</sub>H, -Cl, -F, -Br, -I, -NO<sub>2</sub>, -CN, =O, -OH, -perfluoro C<sub>1-3</sub> alkyl, R<sub>5</sub>, -OR<sub>5</sub>, -NHR<sub>5</sub>, OR<sub>9</sub>,  
 15 -N(R<sub>9</sub>)(R<sub>10</sub>), R<sub>9</sub>, -C(O)-R<sub>10</sub>, and



20 provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub> group which comprises one or more additional -Ar<sub>3</sub> groups, said additional -Ar<sub>3</sub> groups are not substituted with another -Ar<sub>3</sub>;

Compounds of another form of embodiment (I)  
 25 (form 1) are those of formula (V):



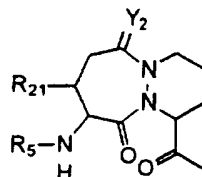
wherein:

m is 1 or 2;

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R<sub>1</sub> is:

(e10-B)

R<sub>3</sub> is selected from the group consisting of:

- CN,
- C(O)-H,
- C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>,
- C(O)-CH<sub>2</sub>-F,
- C=N-O-R<sub>9</sub>, and
- CO-Ar<sub>2</sub>;

5 each R<sub>5</sub> is -C(O)C(O)-OR<sub>10</sub>;

Y<sub>2</sub> is H<sub>2</sub> or O;

each T<sub>1</sub> is independently selected from the group  
consisting of -O-, -S-, -S(O)-, and -S(O)<sub>2</sub>-;

15

R<sub>8</sub> is selected from the group consisting of:

- C(O)-R<sub>10</sub>,
- C(O)O-R<sub>9</sub>,
- C(O)-NH-R<sub>10</sub>,
- 20 -S(O)<sub>2</sub>-R<sub>9</sub>,
- S(O)<sub>2</sub>-NH-R<sub>10</sub>,
- C(O)-CH<sub>2</sub>-OR<sub>10</sub>,
- C(O)C(O)-R<sub>10</sub>,
- C(O)-CH<sub>2</sub>-N(R<sub>10</sub>)(R<sub>10</sub>),
- 25 -C(O)-CH<sub>2</sub>C(O)-O-R<sub>9</sub>,
- C(O)-CH<sub>2</sub>C(O)-R<sub>9</sub>,
- H, and
- C(O)-C(O)-OR<sub>10</sub>;

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each  $R_9$  is independently selected from the group consisting of  $-Ar_3$  and a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$ , wherein the  $-C_{1-6}$  alkyl group is optionally unsaturated;

5        each  $R_{10}$  is independently selected from the group consisting of  $-H$ ,  $-Ar_3$ , a  $C_{3-6}$  cycloalkyl group, and a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$ , wherein the  $-C_{1-6}$  alkyl group is optionally unsaturated;

10        each  $R_{11}$  is independently selected from the group consisting of:

$-Ar_4$ ,  
 $-(CH_2)_{1-3}-Ar_4$ ,  
 $-H$ , and

15         $-C(O)-Ar_4$ ;

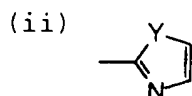
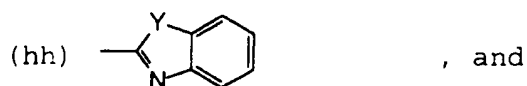
$R_{15}$  is selected from the group consisting of  $-OH$ ,  $-OAr_3$ ,  $-N(H)-OH$ , and  $-OC_{1-6}$ , wherein  $C_{1-6}$  is a straight or branched alkyl group optionally substituted with  $Ar_3$ ,  $-CONH_2$ ,  $-OR_5$ ,  $-OH$ ,  $-OR_9$ , or  $-CO_2H$ ;

20        each  $R_{21}$  is independently selected from the group consisting of  $-H$  or a  $-C_{1-6}$  straight or branched alkyl group;

$Ar_2$  is independently selected from the following group, in which any ring may optionally be singly or  
25        multiply substituted by  $-Q_1$  or phenyl, optionally substituted by  $Q_1$ ;



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5 wherein each Y is independently selected from the group consisting of O and S;

each Ar<sub>3</sub> is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, and -NH-, -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

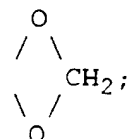
each Ar<sub>4</sub> is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, -NH-, -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

30 each Q<sub>1</sub> is independently selected from the group

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consisting of  $-NH_2$ ,  $-CO_2H$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-I$ ,  $-NO_2$ ,  $-CN$ ,  $=O$ ,  $-OH$ ,  $-perfluoro\ C_{1-3}\ alkyl$ ,  $R_5$ ,  $-OR_5$ ,  $-NHR_5$ ,  $OR_9$ ,  $-N(R_9)(R_{10})$ ,  $R_9$ ,  $-C(O)-R_{10}$ , and  $O$

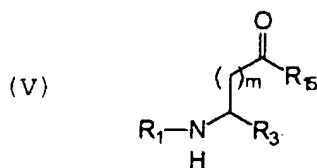
5



provided that when  $-Ar_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-Ar_3$  groups, said additional  $-Ar_3$  groups are not substituted with another  $-Ar_3$ ;

Alternatively, compounds of this form of embodiment I (form 2) are those wherein  $R_{21}$  is  $-CH_3$ .

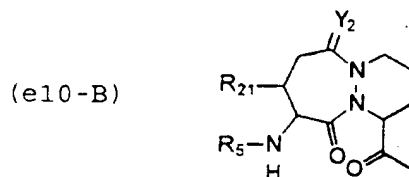
Compounds of another form of embodiment (J) (form  
15 1) are those of formula (V):



wherein:

m is 1 or 2;

20  $R_1$  is:



$R_3$  is selected from the group consisting of:

-CN,

$$-C(O)-H,$$

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-C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>,  
 -C(O)-CH<sub>2</sub>-F,  
 -C=N-O-R<sub>9</sub>, and  
 -CO-Ar<sub>2</sub>;

5 each R<sub>5</sub> is independently selected from the group consisting of:

-C(O)-R<sub>10</sub>,  
 -C(O)O-R<sub>9</sub>,  
 -C(O)-N(R<sub>10</sub>)(R<sub>10</sub>)  
 10 -S(O)<sub>2</sub>-R<sub>9</sub>,  
 -S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
 -C(O)-CH<sub>2</sub>-O-R<sub>9</sub>,  
 -C(O)C(O)-R<sub>10</sub>,  
 -R<sub>9</sub>,  
 15 -H,  
 -C(O)C(O)-OR<sub>10</sub>, and  
 -C(O)C(O)-N(R<sub>9</sub>)(R<sub>10</sub>);

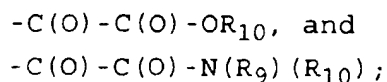
Y<sub>2</sub> is H<sub>2</sub> or O;

20 each T<sub>1</sub> is independently selected from the group consisting of -O-, -S-, -S(O)-, and -S(O)<sub>2</sub>-;

R<sub>8</sub> is selected from the group consisting of:

-C(O)-R<sub>10</sub>,  
 -C(O)O-R<sub>9</sub>,  
 25 -C(O)-NH-R<sub>10</sub>,  
 -S(O)<sub>2</sub>-R<sub>9</sub>,  
 -S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
 -C(O)-CH<sub>2</sub>-OR<sub>10</sub>,  
 -C(O)C(O)-R<sub>10</sub>,  
 30 -C(O)-CH<sub>2</sub>-N(R<sub>10</sub>)(R<sub>10</sub>),  
 -C(O)-CH<sub>2</sub>-C(O)-O-R<sub>9</sub>,  
 -C(O)-CH<sub>2</sub>-C(O)-R<sub>9</sub>,  
 -H,

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each R<sub>9</sub> is independently selected from the group consisting of -Ar<sub>3</sub> and a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, wherein  
5 the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

each R<sub>10</sub> is independently selected from the group consisting of -H, -Ar<sub>3</sub>, a C<sub>3-6</sub> cycloalkyl group, and a -C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, wherein the -C<sub>1-6</sub> alkyl group is  
10 optionally unsaturated;

each R<sub>11</sub> is independently selected from the group consisting of:

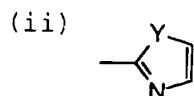
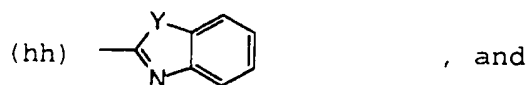
-Ar<sub>4</sub>,  
15 -(CH<sub>2</sub>)<sub>1-3</sub>-Ar<sub>4</sub>,  
-H, and  
-C(O)-Ar<sub>4</sub>;

R<sub>15</sub> is selected from the group consisting of -OH, -OAr<sub>3</sub>, -N(H)-OH, and -OC<sub>1-6</sub>, wherein C<sub>1-6</sub> is a straight or branched alkyl group optionally substituted with Ar<sub>3</sub>,  
20 -CONH<sub>2</sub>, -OR<sub>5</sub>, -OH, -OR<sub>9</sub>, or -CO<sub>2</sub>H;

each R<sub>21</sub> is independently selected from the group consisting of -H or a -C<sub>1-6</sub> straight or branched alkyl group;  
25

Ar<sub>2</sub> is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by -Q<sub>1</sub> or phenyl, optionally substituted by Q<sub>1</sub>:

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5 wherein each Y is independently selected from the group consisting of O and S;

each Ar<sub>3</sub> is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, and -NH-, -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

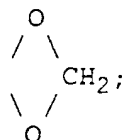
each Ar<sub>4</sub> is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, -NH-, -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

30 each Q<sub>1</sub> is independently selected from the group

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consisting of  $-\text{NH}_2$ ,  $-\text{CO}_2\text{H}$ ,  $-\text{Cl}$ ,  $-\text{F}$ ,  $-\text{Br}$ ,  $-\text{I}$ ,  $-\text{NO}_2$ ,  $-\text{CN}$ ,  
 $=\text{O}$ ,  $-\text{OH}$ ,  $-\text{perfluoro C}_{1-3}$  alkyl,  $\text{R}_5$ ,  $-\text{OR}_5$ ,  $-\text{NHR}_5$ ,  $\text{OR}_9$ ,  
 $-\text{N}(\text{R}_9)(\text{R}_{10})$ ,  $\text{R}_9$ ,  $-\text{C}(\text{O})-\text{R}_{10}$ , and

5



provided that when  $-\text{Ar}_3$  is substituted with a  $\text{Q}_1$   
 group which comprises one or more additional  $-\text{Ar}_3$   
 10 groups, said additional  $-\text{Ar}_3$  groups are not substituted  
 with another  $-\text{Ar}_3$ ;

provided that when:

$m$  is 1;  
 $\text{R}_1$  is  $(\text{e}10)$ ;  
 15  $\text{X}_5$  is  $\text{CH}$ ;  
 $\text{R}_{15}$  is  $-\text{OH}$ ;  
 $\text{R}_{21}$  is  $-\text{H}$ ; and

$\text{Y}_2$  is  $\text{O}$  and  $\text{R}_3$  is  $-\text{C}(\text{O})-\text{H}$ , then  $\text{R}_5$  cannot be:  
 $-\text{C}(\text{O})-\text{R}_{10}$ , wherein  $\text{R}_{10}$  is  $-\text{Ar}_3$  and the  $\text{Ar}_3$  cyclic  
 20 group is phenyl, unsubstituted by  $-\text{Q}_1$ , 4-  
 (carboxymethoxy)phenyl, 2-fluorophenyl, 2-pyridyl, N-  
 (4-methylpiperazino)methylphenyl, or  
 $-\text{C}(\text{O})-\text{OR}_9$ , wherein  $\text{R}_9$  is  $-\text{CH}_2-\text{Ar}_3$ , and the  $\text{Ar}_3$   
 cyclic group is phenyl, unsubstituted by  $-\text{Q}_1$ ; and when

25  $\text{Y}_2$  is  $\text{O}$ ,  $\text{R}_3$  is  $-\text{C}(\text{O})-\text{CH}_2-\text{T}_1-\text{R}_{11}$ ,  $\text{T}_1$  is  $\text{O}$ , and  $\text{R}_{11}$   
 is  $\text{Ar}_4$ , wherein the  $\text{Ar}_4$  cyclic group is 5-(1-(4-  
 chlorophenyl)-3-trifluoromethyl)pyrazolyl), then  $\text{R}_5$   
 cannot be:

30  $-\text{C}(\text{O})-\text{R}_{10}$ , wherein  $\text{R}_{10}$  is  $-\text{Ar}_3$  and the  $\text{Ar}_3$  cyclic  
 group is 4-(dimethylaminomethyl)phenyl, phenyl, 4-  
 (carboxymethylthio)phenyl, 4-(carboxyethylthio)phenyl,  
 4-(carboxyethyl)phenyl, 4-(carboxypropyl)phenyl, 2-

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fluorophenyl, 2-pyridyl, N-(4-methylpiperazino)methylphenyl, or

-C(O)-OR<sub>9</sub>, wherein R<sub>9</sub> is -CH<sub>2</sub>-Ar<sub>3</sub> and the Ar<sub>3</sub> cyclic group is phenyl;

5 and when R<sub>11</sub> is Ar<sub>4</sub>, wherein the Ar<sub>4</sub> cyclic group is 5-(1-phenyl-3-trifluoromethyl)pyrazolyl, then R<sub>5</sub> cannot be:

-C(O)-OR<sub>9</sub>, wherein R<sub>9</sub> is -CH<sub>2</sub>-Ar<sub>3</sub>, and the Ar<sub>3</sub> cyclic group is phenyl;

10 and when R<sub>11</sub> is Ar<sub>4</sub>, wherein the Ar<sub>4</sub> cyclic group is 5-(1-(2-pyridyl)-3-trifluoromethyl)pyrazolyl, then R<sub>5</sub> cannot be:

-C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is -Ar<sub>3</sub> and the Ar<sub>3</sub> cyclic group is 4-(dimethylaminomethyl)phenyl, or

15 -C(O)-OR<sub>9</sub>, wherein R<sub>9</sub> is -CH<sub>2</sub>-Ar<sub>3</sub>, and the Ar<sub>3</sub> cyclic group is phenyl, unsubstituted by -Q<sub>1</sub>,; and when

Y<sub>2</sub> is O, R<sub>3</sub> is -C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>, T<sub>1</sub> is O, and R<sub>11</sub> is -C(O)-Ar<sub>4</sub>, wherein the Ar<sub>4</sub> cyclic group is 2,5-dichlorophenyl, then R<sub>5</sub> cannot be:

20 -C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is -Ar<sub>3</sub> and the Ar<sub>3</sub> cyclic group is 4-(dimethylaminomethyl)phenyl, 4-(N-morpholinomethyl)phenyl, 4-(N-methylpiperazino)methylphenyl, 4-(N-methylimidazolylmethyl)phenyl, 5-benzimidazolyl, 5-benztriazolyl, N-carboethoxy-5-benztriazolyl, N-carboethoxy-5-benzimidazolyl, or

25 -C(O)-OR<sub>9</sub>, wherein R<sub>9</sub> is -CH<sub>2</sub>-Ar<sub>3</sub>, and the Ar<sub>3</sub> cyclic group is phenyl, unsubstituted by -Q<sub>1</sub>,; and when

30 Y<sub>2</sub> is H<sub>2</sub>, R<sub>3</sub> is -C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>, T<sub>1</sub> is O, and R<sub>11</sub> is

-C(O)-Ar<sub>4</sub>, wherein the Ar<sub>4</sub> cyclic group is 2,5-dichlorophenyl, then R<sub>5</sub> cannot be:

-C(O)-OR<sub>9</sub>, wherein R<sub>9</sub> is -CH<sub>2</sub>-Ar<sub>3</sub> and the Ar<sub>3</sub>

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cyclic group is phenyl.

Compounds of another form of embodiment J (form 2) are those wherein  $R_{21}$  is  $-\text{CH}_3$ .

Compounds of another form of embodiment J (form 3)  
5 are those wherein  $R_5$  is  $-\text{C}(\text{O})-\text{C}(\text{O})-\text{OR}_{10}$ .

Compounds of another form of embodiment J (form 4) are those wherein  $R_5$  is  $-\text{C}(\text{O})-\text{C}(\text{O})-\text{OR}_{10}$  and  $R_{21}$  is  $-\text{CH}_3$ .

Preferred compounds of embodiments H, I, and J employ formula (V), wherein  $R_3$  is  $-\text{CO}-\text{Ar}_2$ .

10 More preferably, when  $R_3$  is  $-\text{CO}-\text{Ar}_2$  Y is O.

Preferred compounds of embodiments H, I, and J employ formula (V), wherein  $R_3$  is  $-\text{C}(\text{O})-\text{CH}_2-\text{T}_1-\text{R}_{11}$  and  $\text{R}_{11}$  is  $-(\text{CH}_2)_{1-3}-\text{Ar}_4$ .

15 More preferably, when  $R_3$  is  $-\text{C}(\text{O})-\text{CH}_2-\text{T}_1-\text{R}_{11}$  and  $\text{R}_{11}$  is  $-(\text{CH}_2)_{1-3}-\text{Ar}_4$ ,  $\text{T}_1$  is O.

Preferred compounds of embodiments H, I, and J employ formula (V), wherein  $R_3$  is  $-\text{C}(\text{O})-\text{CH}_2-\text{T}_1-\text{R}_{11}$ ,  $\text{T}_1$  is O, and  $\text{R}_{11}$  is  $-\text{C}(\text{O})-\text{Ar}_4$ .

20 Preferred compounds of embodiments H, I, and J employ formula (V), wherein  $R_3$  is  $-\text{C}(\text{O})-\text{H}$ .

Preferred compounds of embodiments H, I, and J employ formula (V), wherein  $R_3$  is  $-\text{CO}-\text{CH}_2-\text{T}_1-\text{R}_{11}$  and  $\text{R}_{11}$  is  $-\text{Ar}_4$ .

More preferably, when  $R_3$  is  $-\text{CO}-\text{CH}_2-\text{T}_1-\text{R}_{11}$  and



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$R_{11}$  is  $-\text{Ar}_4$ ,  $T_1$  is O or S.

More preferred compounds of embodiments H and J (forms 1 and 2) are those wherein  $R_5$  is selected from the group consisting of:

- 5            $-\text{C}(\text{O})-\text{R}_{10}$ ,  
             $-\text{C}(\text{O})\text{O}-\text{R}_9$ , and  
             $-\text{C}(\text{O})-\text{NH}-\text{R}_{10}$ .

Alternatively, more preferred compounds of embodiments H and J (forms 1 and 2) are those wherein  $R_5$  is selected from the group consisting of:

- 10            $-\text{S}(\text{O})_2-\text{R}_9$ ,  
             $-\text{S}(\text{O})_2-\text{NH}-\text{R}_{10}$ ,  
             $-\text{C}(\text{O})-\text{C}(\text{O})-\text{R}_{10}$ ,  
             $-\text{R}_9$ ,  
15            $-\text{C}(\text{O})-\text{C}(\text{O})-\text{OR}_{10}$ , and  
             $-\text{C}(\text{O})-\text{C}(\text{O})-\text{N}(\text{R}_9)(\text{R}_{10})$ .

Most preferably,  $R_5$  is  $-\text{C}(\text{O})-\text{C}(\text{O})-\text{R}_{10}$ .

Alternatively,  $R_5$  is  $-\text{C}(\text{O})-\text{C}(\text{O})-\text{OR}_{10}$ .

20           More preferred compounds of embodiments H, I (form 2), and J (forms 2 and 4) are those wherein:

- m is 1;  
25            $Y_2$  is O;

$R_{15}$  is  $-\text{OH}$  or  $-\text{OC}_{1-4}$  straight or branched alkyl group optionally substituted with  $\text{Ar}_3$ ,  $-\text{OH}$ ,  $-\text{OR}_9$ ,  $-\text{CO}_2\text{H}$ ,  
30           wherein the  $R_9$  is a  $\text{C}_{1-4}$  branched or straight chain alkyl group; wherein  $\text{Ar}_3$  is morpholinyl or phenyl, wherein the phenyl is optionally substituted with  $\text{Q}_1$ ;

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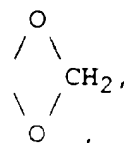
Ar<sub>2</sub> is (hh);

Y is O, and

each Ar<sub>3</sub> cyclic group is independently selected  
 5 from the set consisting of phenyl, naphthyl, thienyl,  
 quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl,  
 isoxazolyl, benzotriazolyl, benzimidazolyl,  
 thienothienyl, imidazolyl, thiadiazolyl,  
 benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl,  
 10 and said cyclic group optionally being singly or  
 multiply substituted by -Q<sub>1</sub>;

each Ar<sub>4</sub> cyclic group is independently selected  
 from the group consisting of phenyl, tetrazolyl,  
 pyridyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl,  
 15 and said cyclic group optionally being singly or  
 multiply substituted by -Q<sub>1</sub>;

each Q<sub>1</sub> is independently selected from the group  
 consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub>  
 wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is  
 20 -C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -N(R<sub>9</sub>)(R<sub>10</sub>), and



25

wherein each R<sub>9</sub> and R<sub>10</sub> are independently a -C<sub>1-6</sub>  
 straight or branched alkyl group optionally substituted  
 with Ar<sub>3</sub> wherein the Ar<sub>3</sub> cyclic group is phenyl, and  
 said cyclic group optionally being singly or multiply  
 30 substituted by -Q<sub>1</sub>;

provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub>  
 group which comprises one or more additional -Ar<sub>3</sub>  
 groups, said additional -Ar<sub>3</sub> groups are not substituted

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with another  $-Ar_3$ .

More preferred compounds of embodiments I (form 1), and J (form 3) are those wherein:

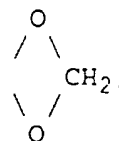
m is 1;

5  $R_{21}$  is  $-H$  or  $-CH_3$ ;

$R_{51}$  is a  $C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$ , wherein the  $Ar_3$  cyclic group is phenyl, said cyclic group optionally being multiply or singly substituted by  $-Q_1$ ;

10 each  $Ar_3$  cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinoliny, isoquinoliny, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl,  
15 benzo[b]thiophenyl, pyridyl, benzofuranyl, or indolyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

each  $Q_1$  is independently selected from the group consisting of  $-NH_2$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-OH$ ,  $-R_9$ ,  $-NH-R_5$   
20 wherein  $R_5$  is  $-C(O)-R_{10}$  or  $-S(O)_2-R_9$ ,  $-OR_5$  wherein  $R_5$  is  $-C(O)-R_{10}$ ,  $-OR_9$ ,  $-N(R_9)(R_{10})$ , and



25

wherein each  $R_9$  and  $R_{10}$  are independently a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$ , wherein the  $Ar_3$  cyclic group is phenyl, and  
30 said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

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provided that when  $-Ar_3$  is substituted with a  $-Q_1$  group which comprises one or more additional  $-Ar_3$  groups, said additional  $-Ar_3$  groups are not substituted with another  $-Ar_3$ .

Preferably, in these more preferred compounds the  $Ar_3$  cyclic group is selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ .

Preferred compounds of embodiments H, and J (forms 1 and 1) are those wherein:

$R_3$  is  $-C(O)-CH_2-T_1-R_{11}$ ;

$T_1$  is O; and

$R_{11}$  is  $-C(O)-Ar_4$ , wherein the  $Ar_4$  cyclic group is selected from the set consisting of tetrazolyl, pyridyl, oxazolyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ .

Preferred compounds of embodiments H, I, and J employ formula (V), wherein  $R_3$  is  $-CO-CH_2-T_1-R_{11}$ ,  $R_{11}$  is  $-Ar_4$ , wherein the  $Ar_4$  cyclic group is pyridyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ .

Preferred compounds of embodiment J (form 1) are those wherein:

$R_3$  is  $-C(O)-H$ , and

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R<sub>5</sub> is -C(O)-R<sub>10</sub>, wherein:

R<sub>10</sub> is Ar<sub>3</sub>, wherein the Ar<sub>3</sub> cyclic group is phenyl optionally being singly or multiply substituted by:

-F,

5 -Cl,

-N(H)-R<sub>5</sub>, wherein -R<sub>5</sub> is -H or -C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is a -C<sub>1-6</sub> straight or branched alkyl group

optionally substituted with Ar<sub>3</sub>, wherein Ar<sub>3</sub> is phenyl,

10 -N(R<sub>9</sub>)(R<sub>10</sub>), wherein R<sub>9</sub> and R<sub>10</sub> are independently a -C<sub>1-4</sub> straight or branched alkyl group, or

-O-R<sub>5</sub>, wherein R<sub>5</sub> is H or a -C<sub>1-4</sub> straight or branched alkyl group.

15 More preferably, Ar<sub>3</sub> is phenyl being optionally singly or multiply substituted at the 3- or 5-position by -Cl or at the 4-position by -NH-R<sub>5</sub>, -N(R<sub>9</sub>)(R<sub>10</sub>), or -O-R<sub>5</sub>.

Other more preferred compounds of embodiment J (form 1) are those wherein:

R<sub>3</sub> is -C(O)-H;

20 R<sub>5</sub> is -C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is Ar<sub>3</sub> and the Ar<sub>3</sub> cyclic group is selected from the group consisting of indolyl, benzimidazolyl, thienyl, and benzo[b]thiophenyl, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

25 Other more preferred compounds of embodiment J (form 1) are those wherein:

R<sub>3</sub> is -C(O)-H;

R<sub>5</sub> is -C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is Ar<sub>3</sub> and the Ar<sub>3</sub>

- 200 -

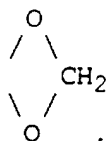
cyclic group is selected from quinolyl and isoquinolyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ .

Other more preferred compounds of embodiment J  
5 (form 1) are those wherein:

$R_3$  is  $-C(O)-H$ ;

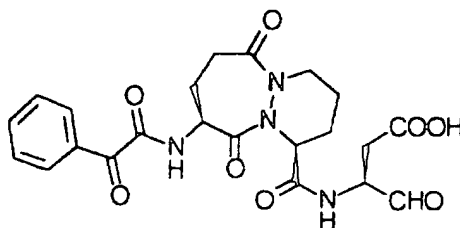
$R_5$  is  $-C(O)-R_{10}$ , wherein  $R_{10}$  is  $Ar_3$  and the  $Ar_3$   
cyclic group is phenyl, substituted by

10

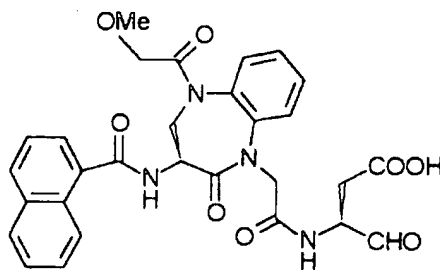


Preferred compounds of embodiment (J)  
15 include, but are not limited to:

2002

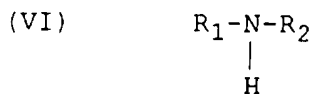


2201



- 201 -

The ICE inhibitors of another embodiment (K) of this invention are those of formula:

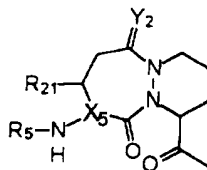


5

wherein:

$R_1$  is:

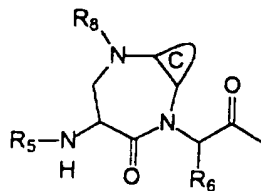
(e10)



, or

10

(w2)

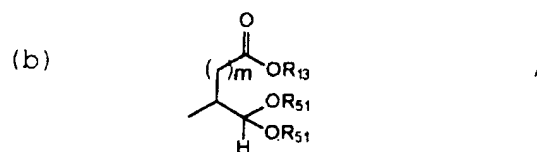
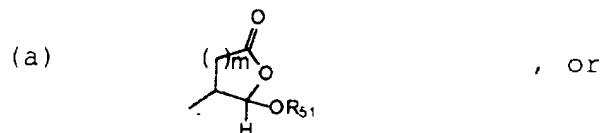


;

C is a ring chosen from the set consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl; the ring optionally being  
15 singly or multiply substituted by  $-Q_1$ ;

$R_2$  is:

- 202 -



m is 1 or 2;

5 each R<sub>5</sub> is independently selected from the group consisting of:

- C(O)-R<sub>10</sub>,
- C(O)O-R<sub>9</sub>,
- C(O)-N(R<sub>10</sub>)(R<sub>10</sub>)
- 10 -S(O)<sub>2</sub>-R<sub>9</sub>,
- S(O)<sub>2</sub>-NH-R<sub>10</sub>,
- C(O)-CH<sub>2</sub>-O-R<sub>9</sub>,
- C(O)C(O)-R<sub>10</sub>,
- R<sub>9</sub>,
- 15 -H,
- C(O)C(O)-OR<sub>10</sub>, and
- C(O)C(O)-N(R<sub>9</sub>)(R<sub>10</sub>);

X<sub>5</sub> is CH or N;

20

Y<sub>2</sub> is H<sub>2</sub> or O;

R<sub>6</sub> is selected from the group consisting of -H and -CH<sub>3</sub>;

25

R<sub>8</sub> is selected from the group consisting of:



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5                   -C(O)-R<sub>10</sub>,  
                   -C(O)O-R<sub>9</sub>,  
                   -C(O)-N(H)-R<sub>10</sub>,  
                   -S(O)<sub>2</sub>-R<sub>9</sub>,  
                   -S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
                   -C(O)-CH<sub>2</sub>-OR<sub>10</sub>,  
                   -C(O)C(O)-R<sub>10</sub>;  
                   -C(O)-CH<sub>2</sub>N(R<sub>10</sub>)(R<sub>10</sub>),  
 10                  -C(O)-CH<sub>2</sub>C(O)-O-R<sub>9</sub>,  
                   -C(O)-CH<sub>2</sub>C(O)-R<sub>9</sub>,  
                   -H, and  
                   -C(O)-C(O)-OR<sub>10</sub>;

15           each R<sub>9</sub> is independently selected from the group  
           consisting of -Ar<sub>3</sub> and a -C<sub>1-6</sub> straight or branched  
           alkyl group optionally substituted with Ar<sub>3</sub>, wherein  
           the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

20           each R<sub>10</sub> is independently selected from the group  
           consisting of -H, -Ar<sub>3</sub>, a -C<sub>3-6</sub> cycloalkyl group, and a  
           -C<sub>1-6</sub> straight or branched alkyl group optionally  
           substituted with Ar<sub>3</sub>, wherein the -C<sub>1-6</sub> alkyl group is  
           optionally unsaturated;

25           R<sub>13</sub> is selected from the group consisting of H,  
           Ar<sub>3</sub>, and a -C<sub>1-6</sub> straight or branched alkyl group  
           optionally substituted with Ar<sub>3</sub>, -CONH<sub>2</sub>, -OR<sub>5</sub>, -OH,  
           -OR<sub>9</sub>, or -CO<sub>2</sub>H;

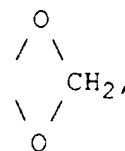
          each R<sub>51</sub> is independently selected from the group  
           consisting of R<sub>9</sub>, -C(O)-R<sub>9</sub>, -C(O)-N(H)-R<sub>9</sub>, or each R<sub>51</sub>  
           taken together forms a saturated 4-8 member carbocyclic  
           ring or heterocyclic ring containing -O-, -S-, or -NH-;

- 204 -

each  $R_{21}$  is independently selected from the group consisting of -H or a  $-C_{1-6}$  straight or branched alkyl group;

each  $Ar_3$  is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-,  $SO_2$ , =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

each  $Q_1$  is independently selected from the group consisting of  $-NH_2$ ,  $-CO_2H$ , -Cl, -F, -Br, -I,  $-NO_2$ , -CN, =O, -OH, -perfluoro  $C_{1-3}$  alkyl,  $R_5$ ,  $-OR_5$ ,  $-NHR_5$ ,  $-OR_9$ ,  $-N(R_9)(R_{10})$ ,  $-R_9$ ,  $-C(O)-R_{10}$ , and



provided that when  $-Ar_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-Ar_3$  groups, said additional  $-Ar_3$  groups are not substituted with another  $-Ar_3$ .

Preferred compounds of this embodiment are those wherein:

m is 1;

- 205 -

C is a ring chosen from the set consisting of benzo, pyrido, or thieno the ring optionally being singly or multiply substituted by halogen, -NH<sub>2</sub>, -NH-R<sub>5</sub>, -NH-R<sub>9</sub>, -OR<sub>10</sub>, or -R<sub>9</sub>, wherein R<sub>9</sub> is a straight or branched C<sub>1-4</sub> alkyl group and R<sub>10</sub> is H or a straight or branched C<sub>1-4</sub> alkyl group;

R<sub>6</sub> is H;

R<sub>13</sub> is H or a C<sub>1-4</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, -OH, -OR<sub>9</sub>, -CO<sub>2</sub>H, wherein the R<sub>9</sub> is a C<sub>1-4</sub> branched or straight chain alkyl group; wherein Ar<sub>3</sub> is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q<sub>1</sub>;

R<sub>21</sub> is -H or -CH<sub>3</sub>;

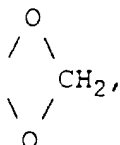
R<sub>51</sub> is a C<sub>1-6</sub> straight or branched alkyl group optionally substituted with Ar<sub>3</sub>, wherein Ar<sub>3</sub> is phenyl, optionally substituted by -Q<sub>1</sub>;

each Ar<sub>3</sub> cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Q<sub>1</sub> is independently selected from the group consisting of -NH<sub>2</sub>, -Cl, -F, -Br, -OH, -R<sub>9</sub>, -NH-R<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub> or -S(O)<sub>2</sub>-R<sub>9</sub>, -OR<sub>5</sub> wherein R<sub>5</sub> is -C(O)-R<sub>10</sub>, -OR<sub>9</sub>, -NHR<sub>9</sub>, and

- 206 -

5



wherein each  $R_9$  and  $R_{10}$  are independently a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$  wherein  $Ar_3$  is phenyl;

10

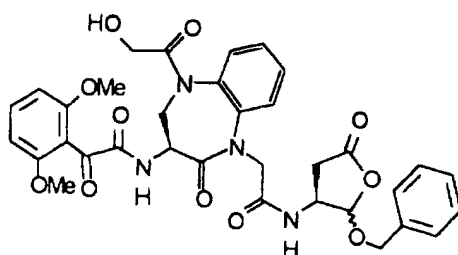
provided that when  $-Ar_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-Ar_3$  groups, said additional  $-Ar_3$  groups are not substituted with another  $-Ar_3$ .

15

Preferably, in this preferred embodiment,  $R_1$  is (w2) and the other substituents are as defined above.

Compounds of this preferred embodiment include, but are not limited to:

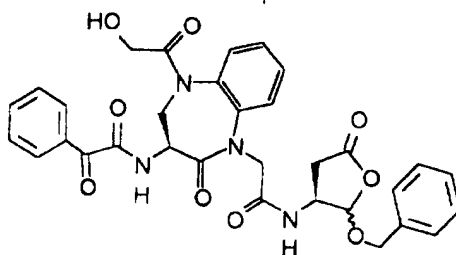
677



; and

20

680



More preferably,  $R_9$  is selected from the

- 207 -

group consisting of:

- C(O)-R<sub>10</sub>,
- C(O)O-R<sub>9</sub>,
- C(O)-CH<sub>2</sub>-OR<sub>10</sub>, and
- C(O)-CH<sub>2</sub>C(O)-R<sub>9</sub>.

Most preferably, R<sub>8</sub> is -C(O)-CH<sub>2</sub>-OR<sub>10</sub> and R<sub>10</sub> is -H or -CH<sub>3</sub>.

Alternatively, in this preferred embodiment, R<sub>1</sub> is (e10) and X<sub>5</sub> is CH and the other substituents are as defined above.

Alternatively, in this preferred embodiment, R<sub>1</sub> is (e10) and X<sub>5</sub> is N and the other substituents are as defined above.

Preferably, in any of the above compounds of embodiment (K), R<sub>5</sub> is -C(O)-R<sub>10</sub> or -C(O)-C(O)-R<sub>10</sub> and the other substituents are as defined above.

More preferably, R<sub>10</sub> is -Ar<sub>3</sub> and the other substituents are as defined above.

More preferably, in these more preferred compounds:

R<sub>5</sub> is -C(O)-R<sub>10</sub> and R<sub>10</sub> is Ar<sub>3</sub>,

wherein the Ar<sub>3</sub> cyclic group is phenyl optionally being singly or multiply substituted by:

-R<sub>9</sub>, wherein R<sub>9</sub> is a C<sub>1-4</sub> straight or branched alkyl group;

-F,

-Cl,

-N(H)-R<sub>5</sub>, wherein -R<sub>5</sub> is -H or -C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is a -C<sub>1-6</sub> straight or branched alkyl group

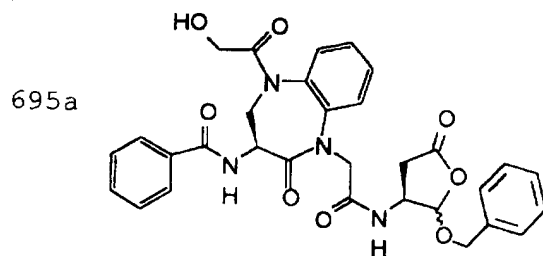
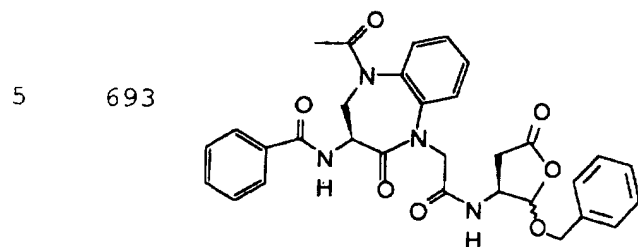
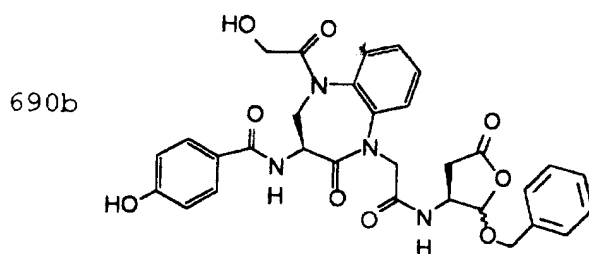
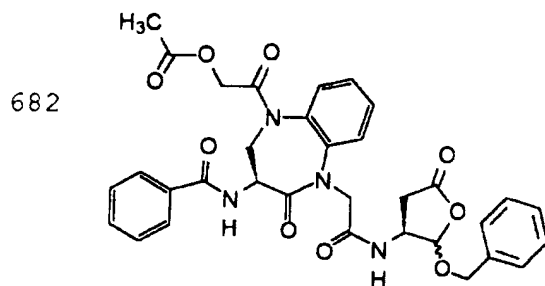
optionally substituted with Ar<sub>3</sub>, wherein Ar<sub>3</sub> is phenyl,

-N(R<sub>9</sub>)(R<sub>10</sub>), wherein R<sub>9</sub> and R<sub>10</sub> are independently a -C<sub>1-4</sub> straight or branched alkyl group, or

-O-R<sub>5</sub>, wherein R<sub>5</sub> is H or a -C<sub>1-4</sub> straight or branched alkyl group.

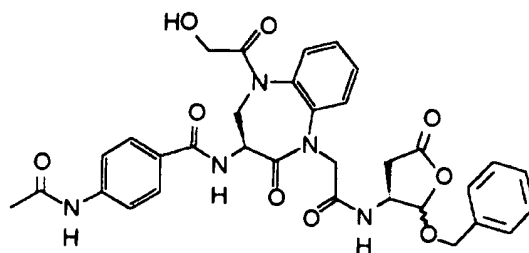
- 208 -

Preferred compounds of this more preferred embodiment include, but are not limited to:



- 209 -

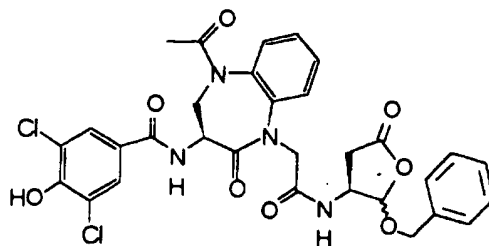
695b



Most preferably,  $Ar_3$  is phenyl  
 being singly or multiply substituted at the 3- or  
 5-position by -Cl or at the 4-position by -NH- $R_5$ ,  
 5 -N( $R_9$ ) ( $R_{10}$ ), or -O- $R_5$ .

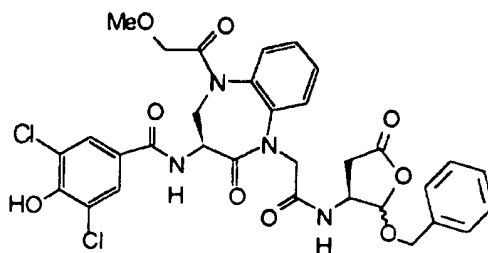
Preferred compounds of this  
 most preferred embodiment include, but are not limited  
 to:

655



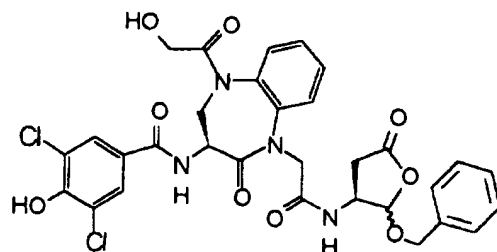
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688a

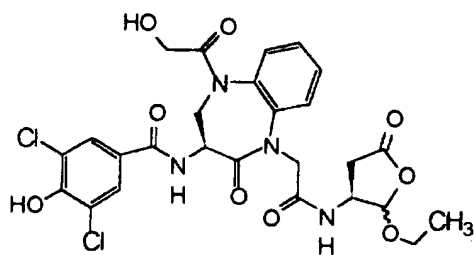


- 210 -

692a

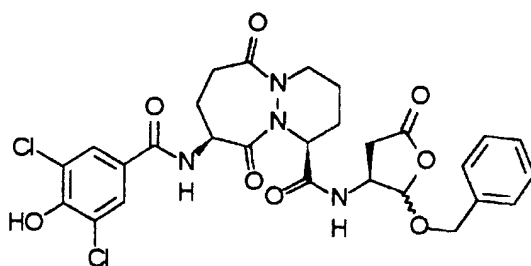


692b



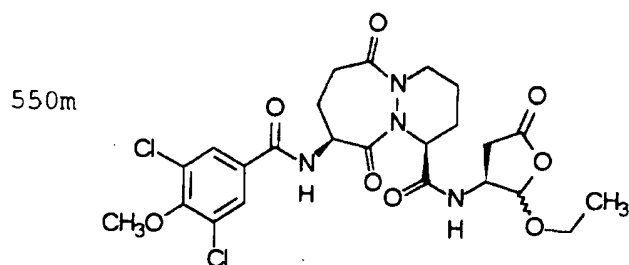
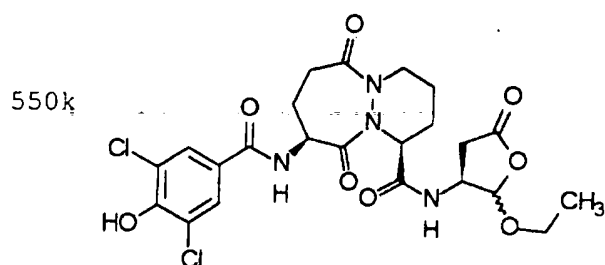
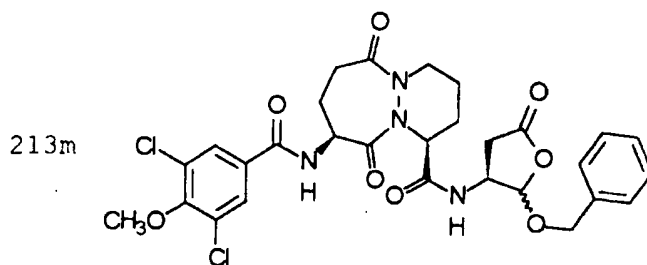
Other preferred compounds of  
this most preferred embodiment include, but are not  
5 limited to:

213k





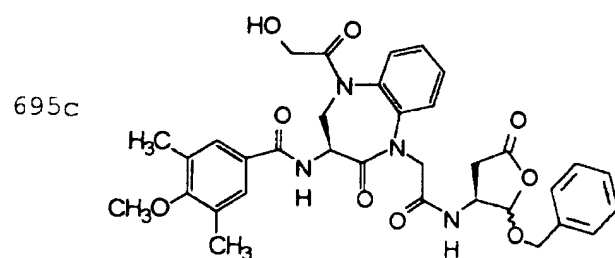
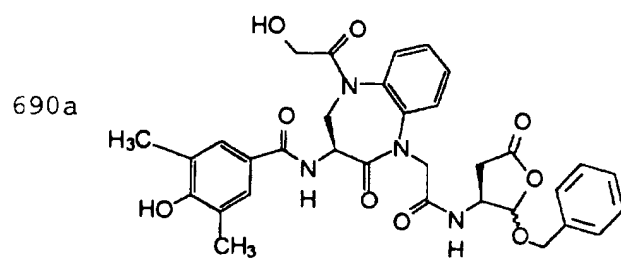
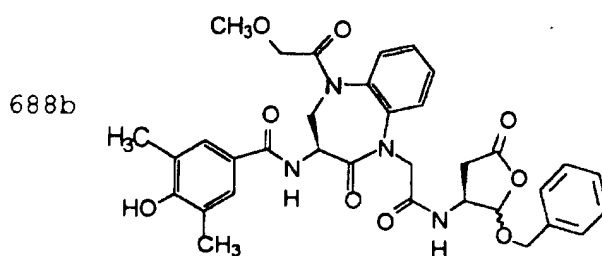
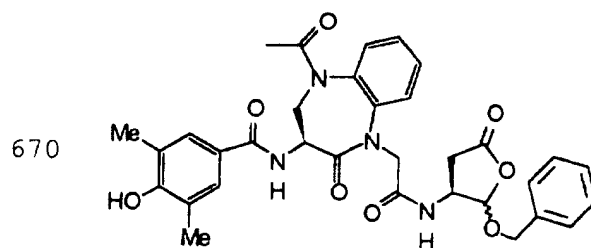
- 211 -



Alternatively, Ar<sub>3</sub> is phenyl being  
 5 singly or multiply substituted at the 3- or 5-position  
 by -R<sub>9</sub>, wherein R<sub>9</sub> is a C<sub>1-4</sub> straight or branched alkyl  
 group; and at the 4-position by -O-R<sub>5</sub>.

Preferred compounds of this  
 most preferred embodiment include, but are not limited  
 10 to:

- 212 -

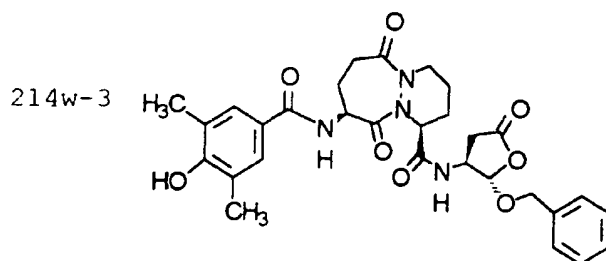
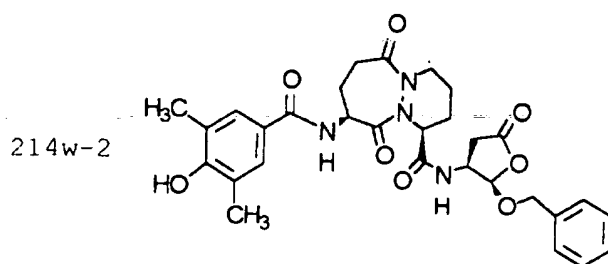
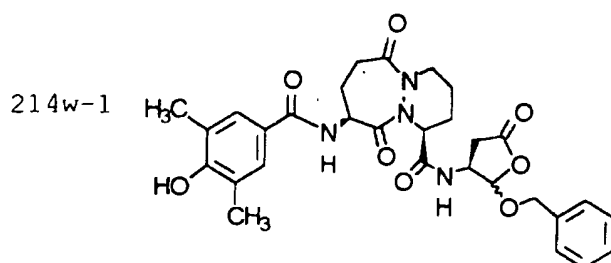


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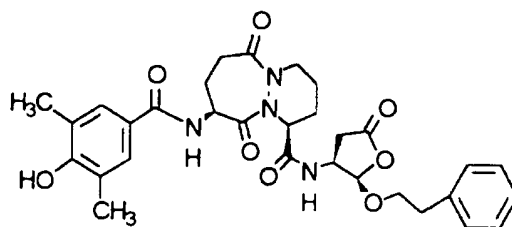
Other preferred compounds of this most preferred embodiment include, but are not

- 213 -

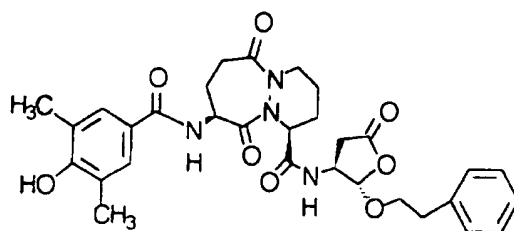
limited to:



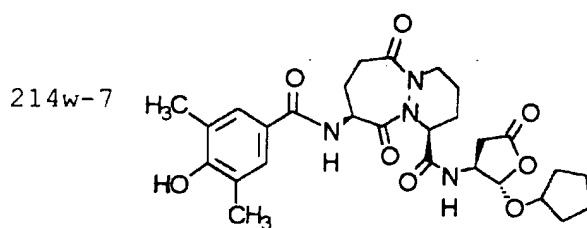
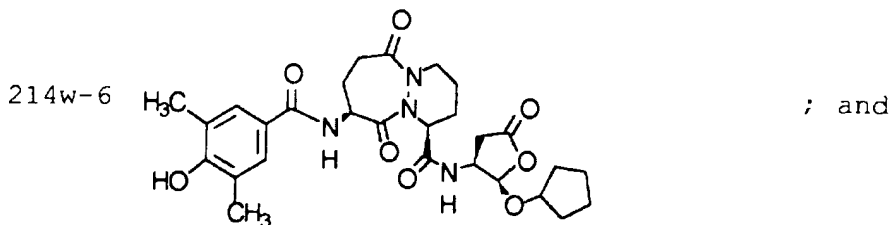
5 214w-4



214w-5



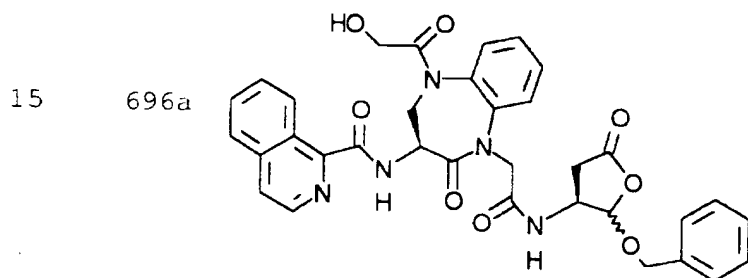
- 214 -



Alternatively, in this more preferred embodiment,  $R_5$  is  $-C(O)-R_{10}$ , wherein  $R_{10}$  is  $Ar_3$  and the  $Ar_3$  cyclic group is selected from the group consisting of is indolyl, benzimidazolyl, thienyl, quinolyl, isoquinolyl and benzo[b]thiophenyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ .

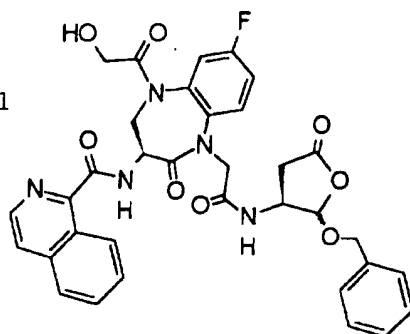
Most preferably, the  $Ar_3$  cyclic group is isoquinolyl.

Preferred compounds of this most preferred embodiment include, but are not limited to:

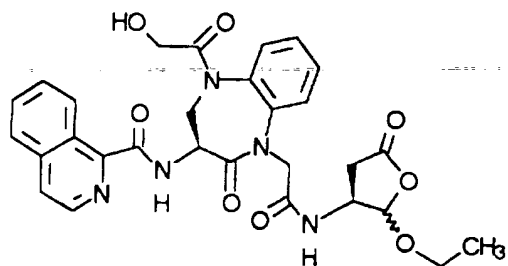


- 215 -

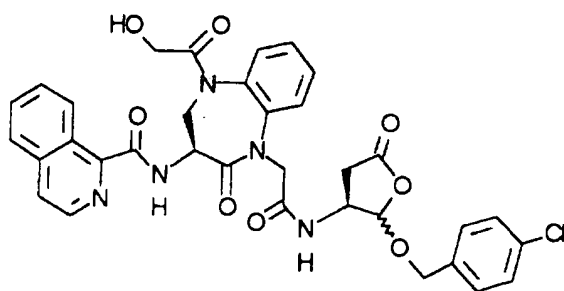
696a-1



696b

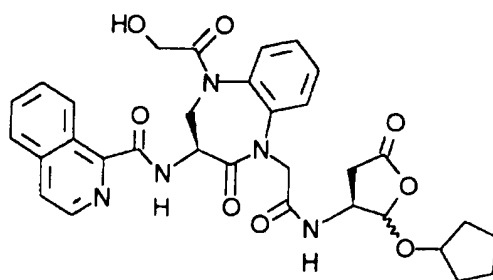


696c

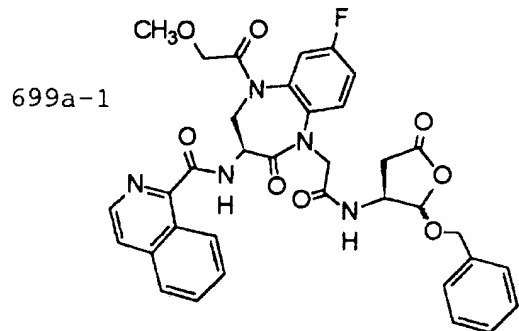
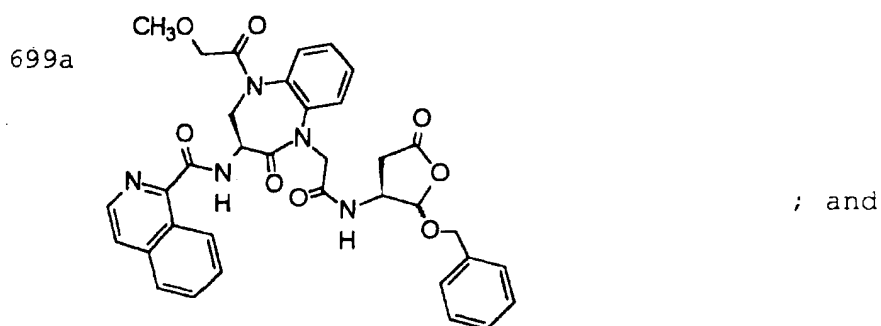
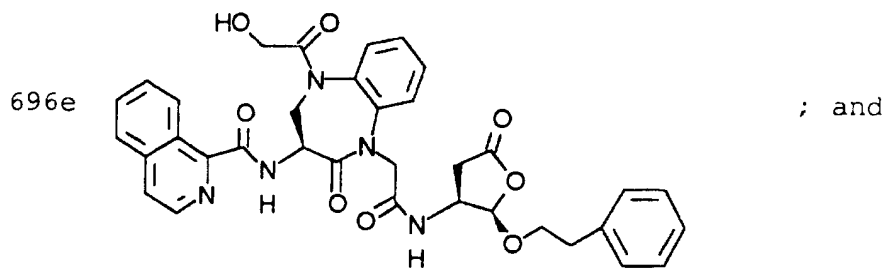


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696d

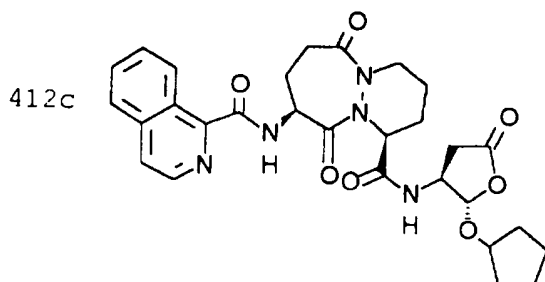
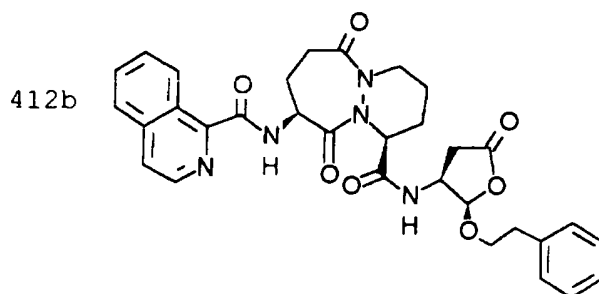
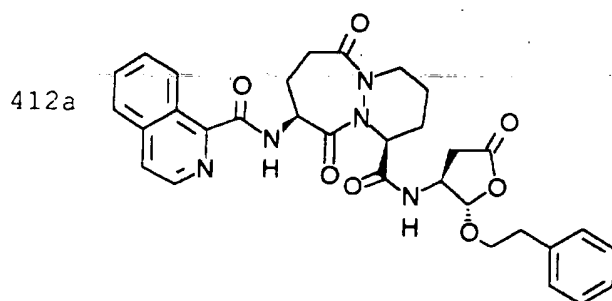
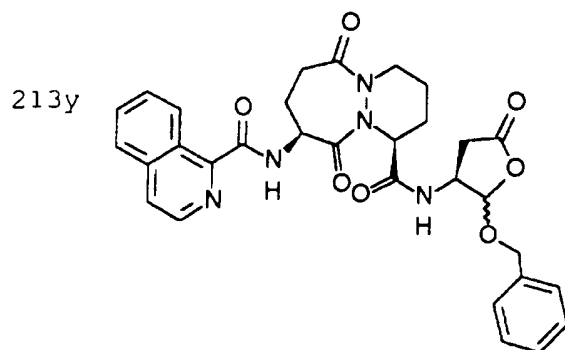


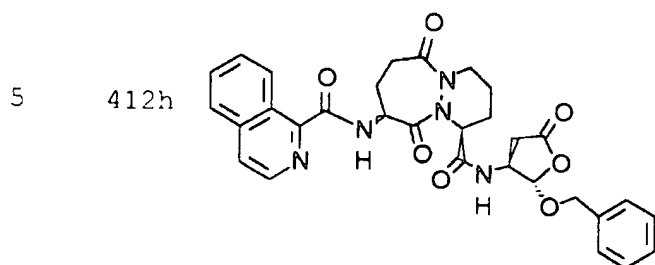
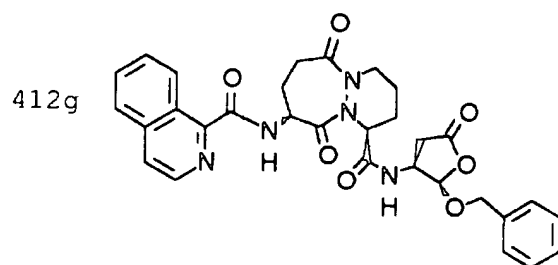
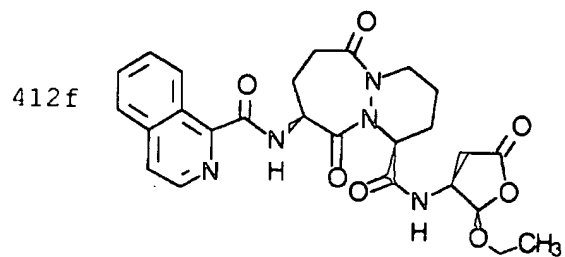
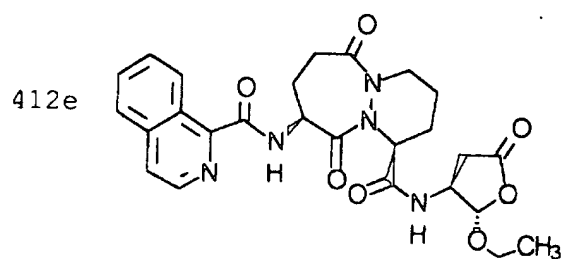
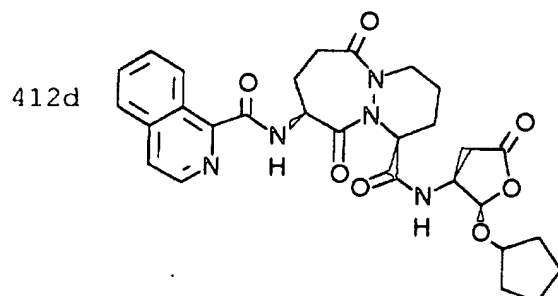
- 216 -



Other preferred compounds of this most preferred embodiment include, but are not limited to:

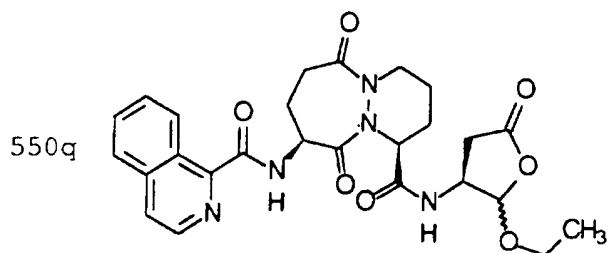
- 217 -



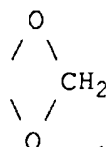




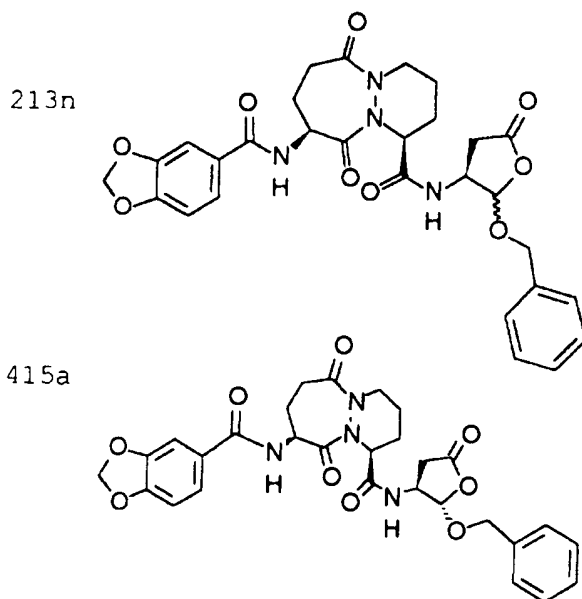
- 219 -



Alternatively, in this more preferred embodiment,  $R_5$  is  $-C(O)-R_{10}$ , wherein  $R_{10}$  is  $Ar_3$  and the  $Ar_3$  cyclic group is phenyl, substituted by



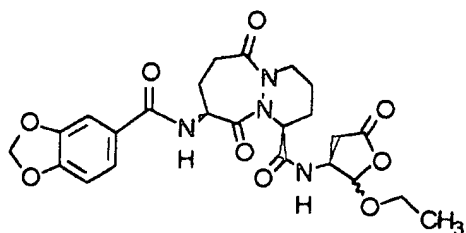
10 Preferred compounds of this more preferred embodiment include, but are not limited to:



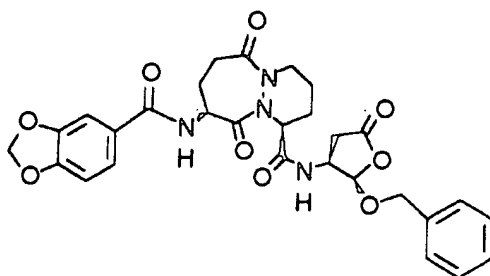
- 220 -

415b

; and

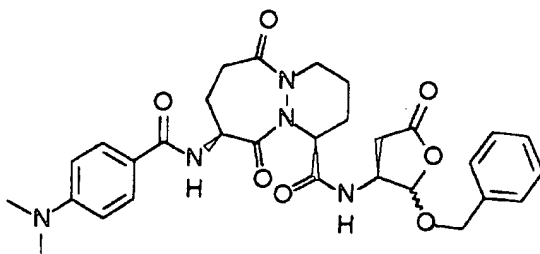


415c

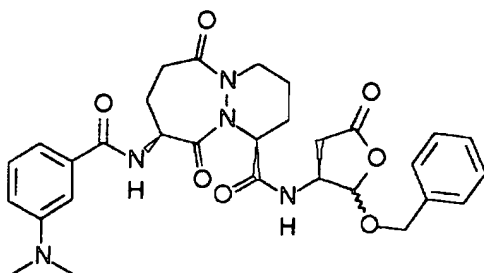


Other compounds of embodiment (K) include,  
5 but are not limited to:

213f

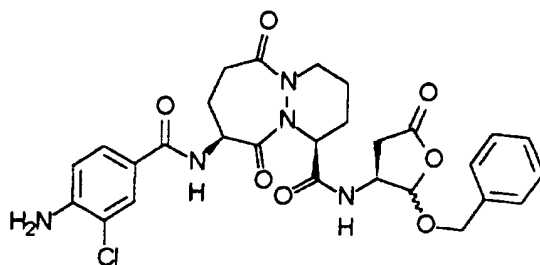


213g

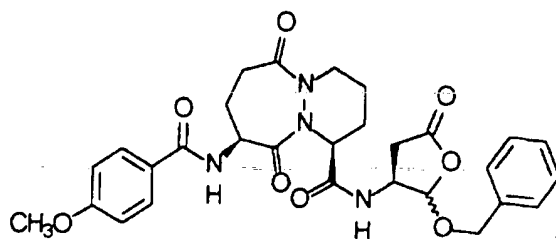


- 221 -

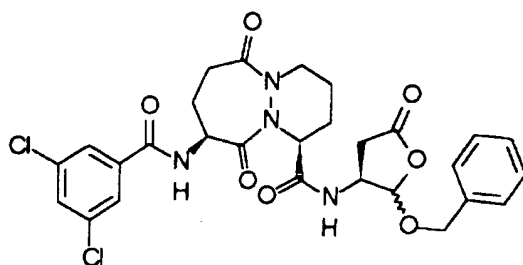
213h



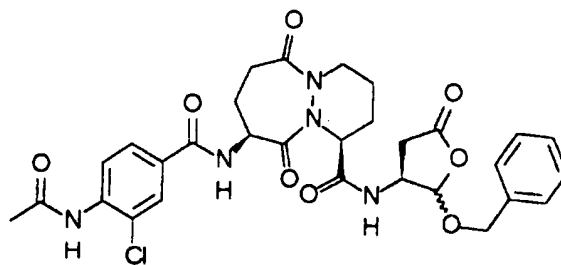
213i



213j

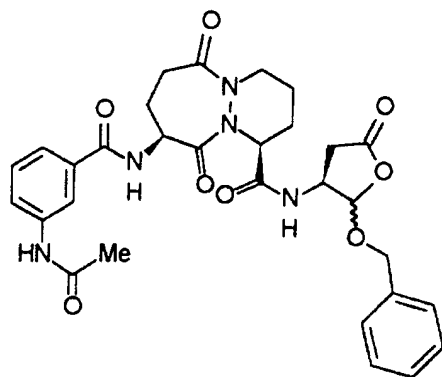


213l

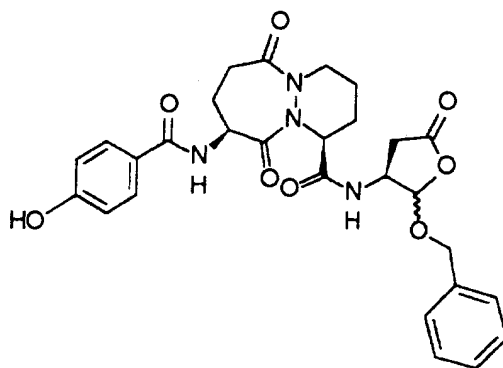


- 222 -

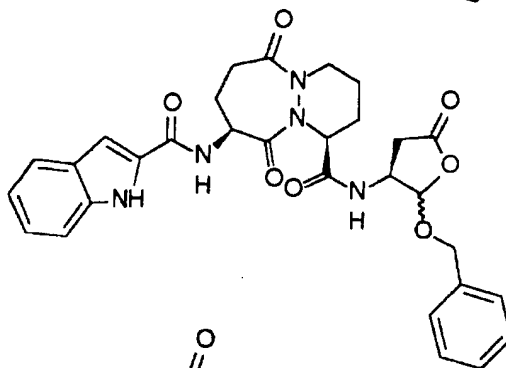
213o



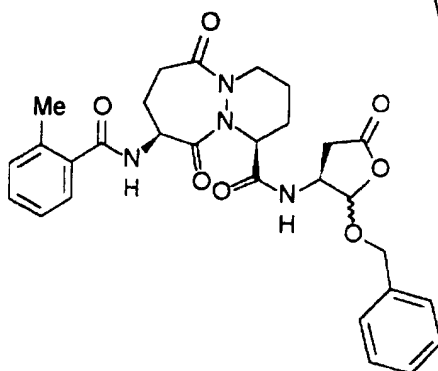
213p



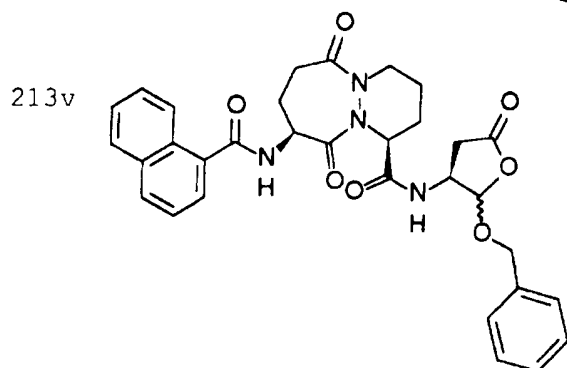
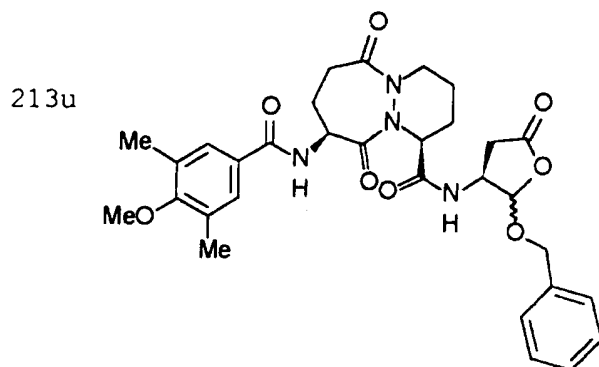
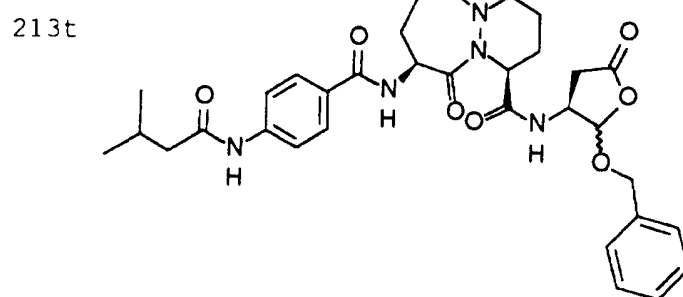
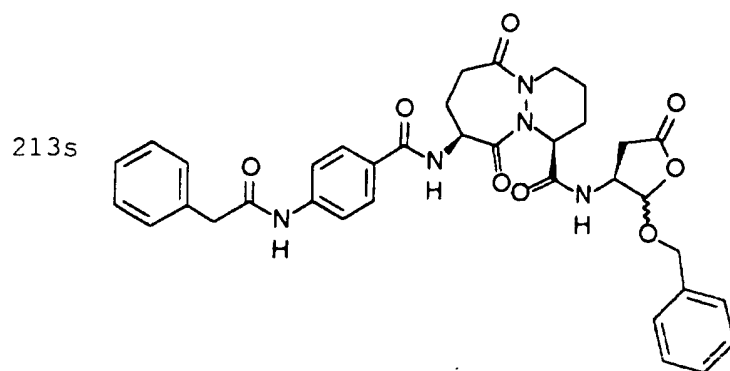
213q



213r

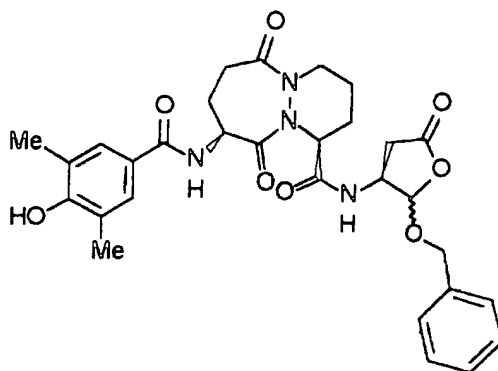


- 223 -

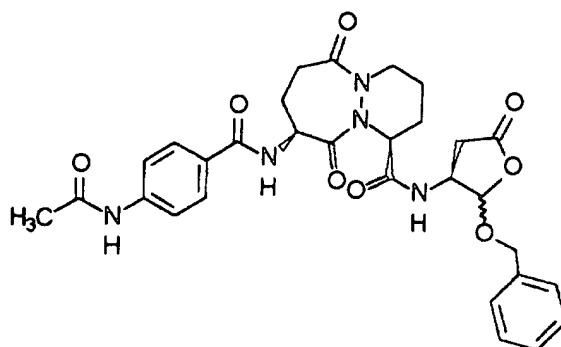


- 224 -

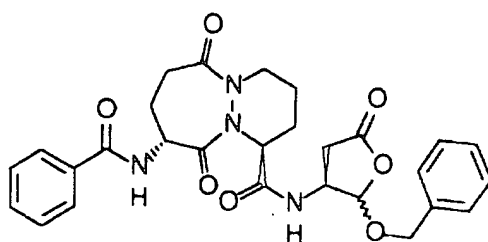
213w



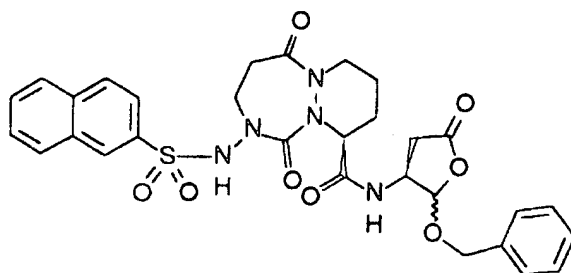
213x



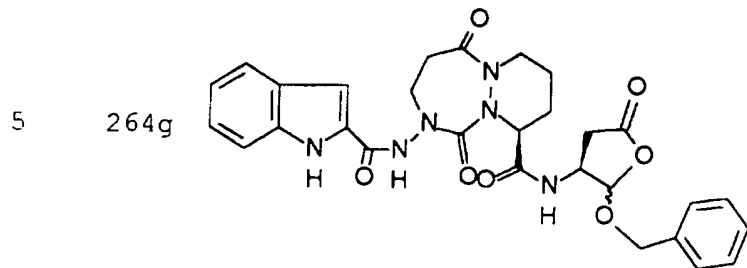
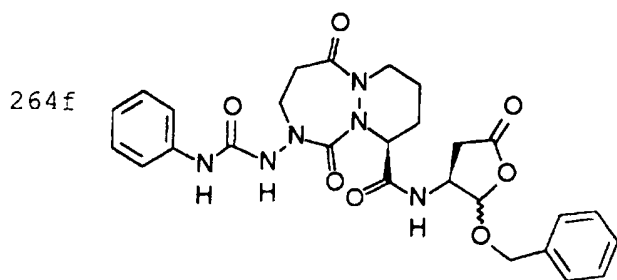
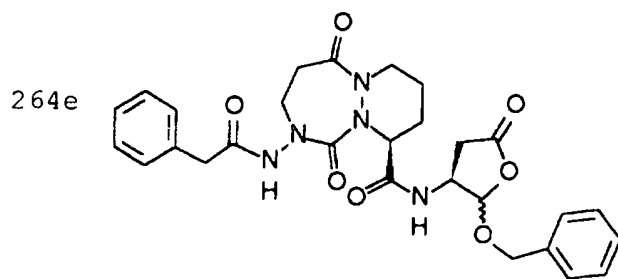
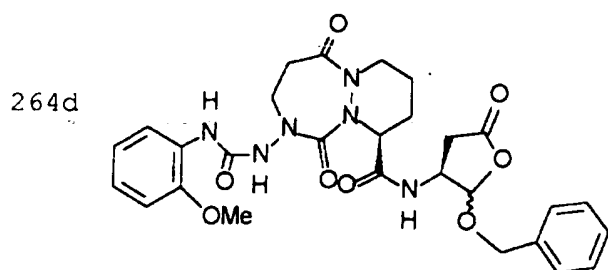
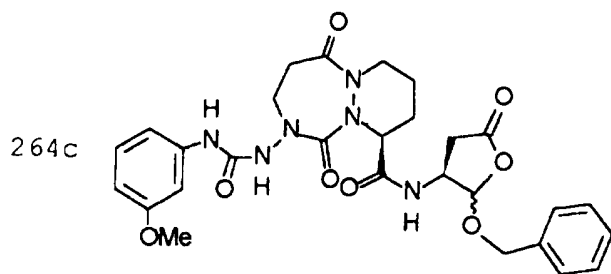
245b



264a

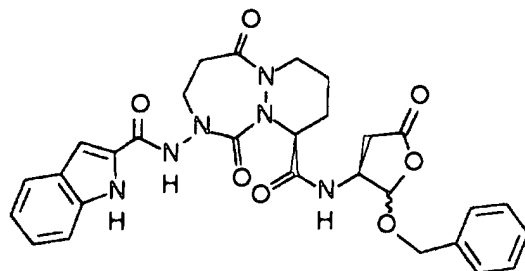


- 225 -

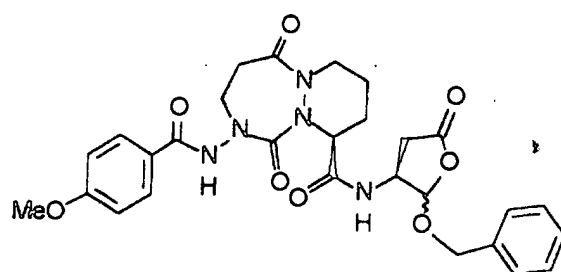


- 226 -

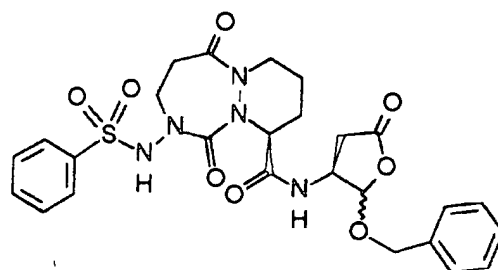
264h



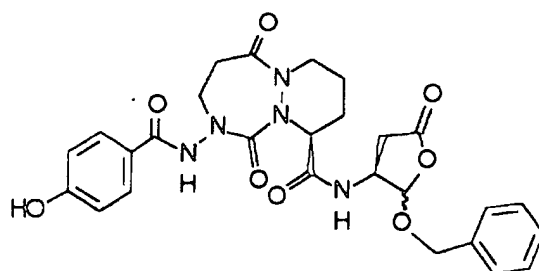
264i



264j

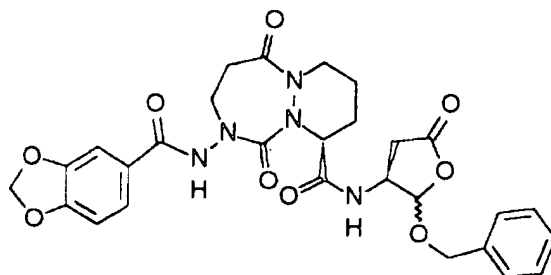


264k



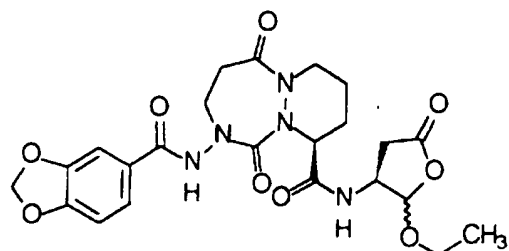
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2641

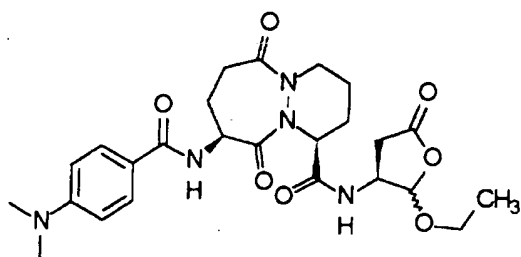




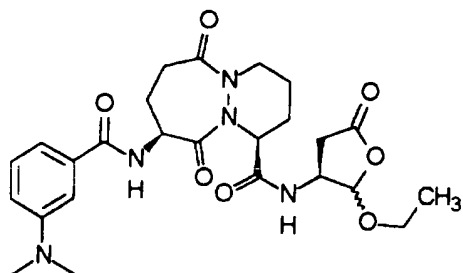
528



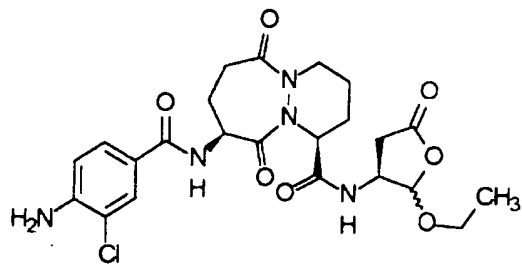
550f



550g

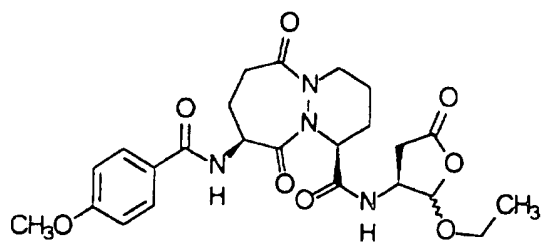


550h



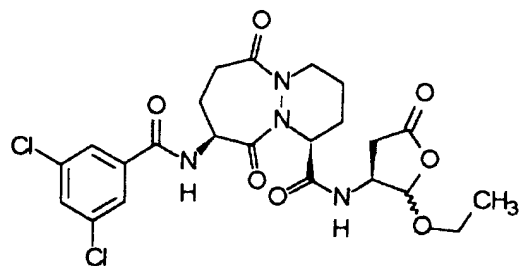
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550i

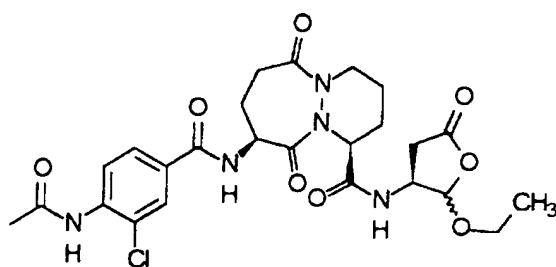


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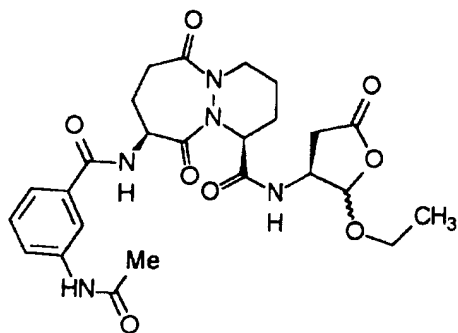
550j



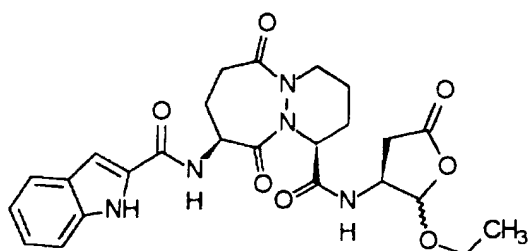
550l



550n

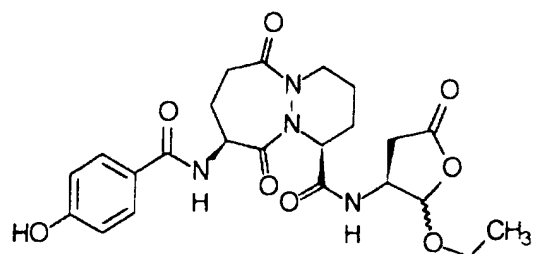


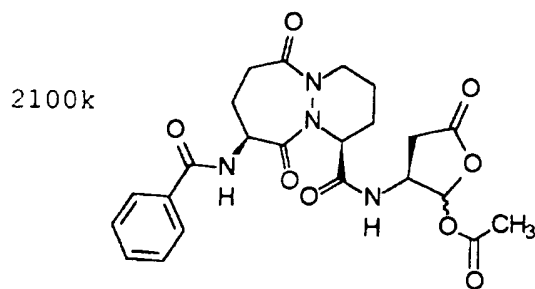
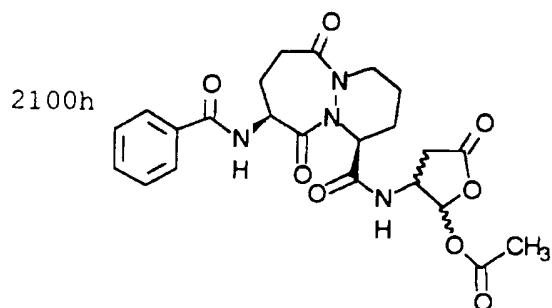
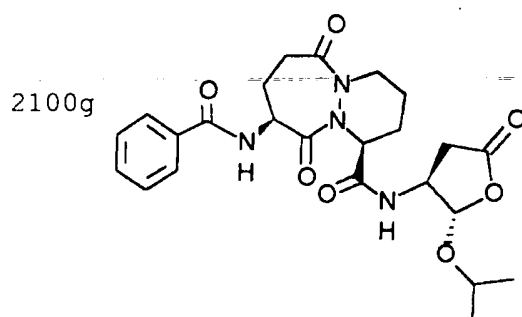
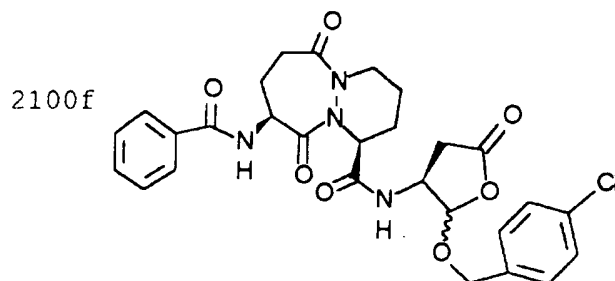
550o



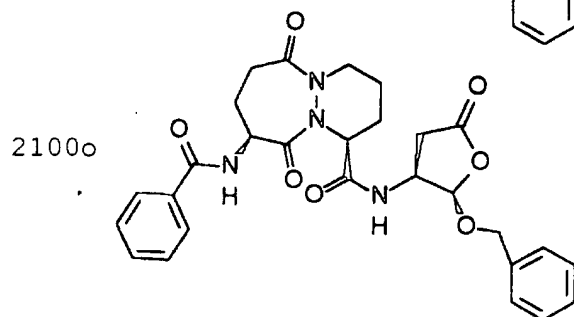
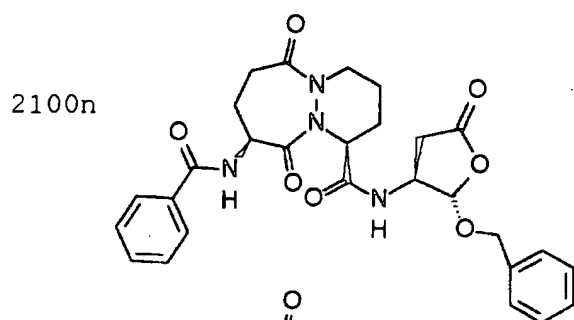
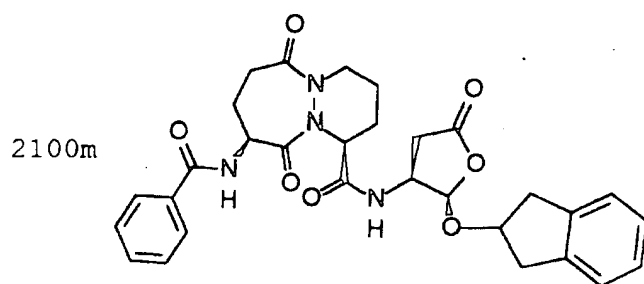
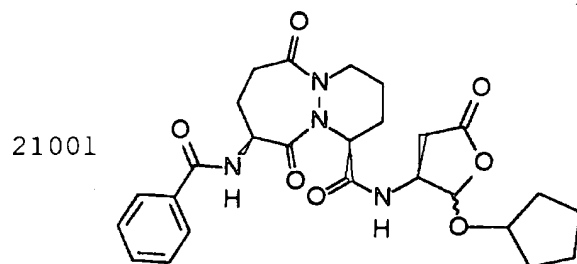
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550p



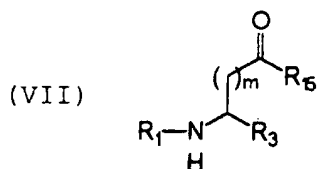


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5                   The ICE inhibitors of another embodiment (L)  
of this invention are those of formula :

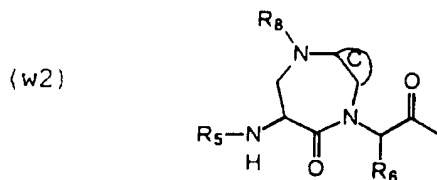
- 231 -



wherein:

m is 1 or 2;

- 5  $R_1$  is selected from the group consisting of the following formulae:



- 10 C is a ring chosen from the set consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl, the ring optionally being singly or multiply substituted by  $-Q_1$ ;

- 15  $R_3$  is selected from the group consisting of:

- CN,  
 -C(O)-H,  
 -C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>,  
 -C(O)-CH<sub>2</sub>-F,  
 20 -C=N-O-R<sub>9</sub>, and  
 -CO-Ar<sub>2</sub>;

each  $R_5$  is independently selected from the group consisting of:

- C(O)-R<sub>10</sub>,  
 25 -C(O)O-R<sub>9</sub>,

- 232 -

-C(O)-N(R<sub>10</sub>)(R<sub>10</sub>)  
 -S(O)<sub>2</sub>-R<sub>9</sub>,  
 -S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
 -C(O)-CH<sub>2</sub>-O-R<sub>9</sub>,  
 5     -C(O)C(O)-R<sub>10</sub>,  
       -R<sub>9</sub>,  
       -H,  
       -C(O)C(O)-OR<sub>10</sub>, and  
       -C(O)C(O)-N(R<sub>9</sub>)(R<sub>10</sub>);

10

each T<sub>1</sub> is independently selected from the group consisting of -O-, -S-, -S(O)-, and -S(O)<sub>2</sub>-;

15     R<sub>6</sub> is selected from the group consisting of -H and  
       -CH<sub>3</sub>;

R<sub>8</sub> is selected from the group consisting of:

-C(O)-R<sub>10</sub>,  
 -C(O)O-R<sub>9</sub>,  
 -C(O)-NH-R<sub>10</sub>,  
 20     -S(O)<sub>2</sub>-R<sub>9</sub>,  
       -S(O)<sub>2</sub>-NH-R<sub>10</sub>,  
       -C(O)-CH<sub>2</sub>-OR<sub>10</sub>,  
       -C(O)C(O)-R<sub>10</sub>,  
       -C(O)-CH<sub>2</sub>-N(R<sub>10</sub>)(R<sub>10</sub>),  
 25     -C(O)-CH<sub>2</sub>C(O)-O-R<sub>9</sub>,  
       -C(O)-CH<sub>2</sub>C(O)-R<sub>9</sub>,  
       -H, and  
       -C(O)-C(O)-OR<sub>10</sub>;

30     each R<sub>9</sub> is independently selected from the group  
       consisting of -Ar<sub>3</sub> and a -C<sub>1-6</sub> straight or branched  
       alkyl group optionally substituted with Ar<sub>3</sub>, wherein  
       the -C<sub>1-6</sub> alkyl group is optionally unsaturated;

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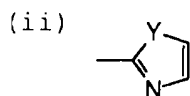
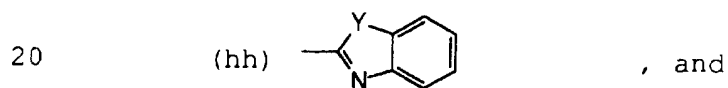
each  $R_{10}$  is independently selected from the group consisting of -H,  $-Ar_3$ , a  $C_{3-6}$  cycloalkyl group, and a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$ , wherein the  $-C_{1-6}$  alkyl group is optionally unsaturated;

each  $R_{11}$  is independently selected from the group consisting of:

- $Ar_4$ ,  
- $(CH_2)_{1-3}-Ar_4$ ,  
-H, and  
-C(O)- $Ar_4$ ;

$R_{15}$  is selected from the group consisting of -OH,  $-OAr_3$ ,  $-N(H)-OH$ , and  $-OC_{1-6}$ , wherein  $C_{1-6}$  is a straight or branched alkyl group optionally substituted with  $Ar_3$ ,  $-CONH_2$ ,  $-OR_5$ ,  $-OH$ ,  $-OR_9$ , or  $-CO_2H$ ;

$Ar_2$  is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by  $-Q_1$  or phenyl, optionally substituted by  $Q_1$ :



wherein each Y is independently selected from the group consisting of O and S;

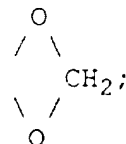
25 each  $Ar_3$  is a cyclic group independently selected from the set consisting of an aryl group which contains

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6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, and -NH-, -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Ar<sub>4</sub> is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO<sub>2</sub>, =N-, -NH-, -N(R<sub>5</sub>)-, and -N(R<sub>9</sub>)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q<sub>1</sub>;

each Q<sub>1</sub> is independently selected from the group consisting of -NH<sub>2</sub>, -CO<sub>2</sub>H, -Cl, -F, -Br, -I, -NO<sub>2</sub>, -CN, =O, -OH, -perfluoro C<sub>1-3</sub> alkyl, R<sub>5</sub>, -OR<sub>5</sub>, -NHR<sub>5</sub>, -OR<sub>9</sub>, -N(R<sub>9</sub>)(R<sub>10</sub>), -R<sub>9</sub>, -C(O)-R<sub>10</sub>, and



provided that when -Ar<sub>3</sub> is substituted with a Q<sub>1</sub> group which comprises one or more additional -Ar<sub>3</sub>



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groups, said additional  $-Ar_3$  groups are not substituted with another  $-Ar_3$ .

Preferably,

m is 1;

5 C is a ring chosen from the set consisting of benzo, pyrido, and thieno, the ring optionally being singly or multiply substituted by halogen,  $-NH_2$ ,  $-NH-R_9$ , or  $-NH-R_9$ ,  $-OR_{10}$ , or  $-R_9$ , wherein  $R_9$  is a straight or branched  $-C_{1-4}$  alkyl group, and  $R_{10}$  is  $-H$  or  
10 a straight or branched  $-C_{1-4}$  alkyl group;

$T_1$  is O or S;

$R_6$  is H;

$R_{11}$  is selected from the group consisting of  $-Ar_4$ ,  
15  $-(CH_2)_{1-3}-Ar_4$ , and  $-C(O)-Ar_4$ ;

$Ar_2$  is (hh);

Y is O;

each  $Ar_3$  cyclic group is independently selected  
20 from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, thiazolyl, benzimidazolyl, thienothienyl, thiadiazolyl, benzotriazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply  
25 substituted by  $-Q_1$ ;

each  $Ar_4$  cyclic group is independently selected from the set consisting of phenyl, tetrazolyl,

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naphthyl, pyridinyl, oxazolyl, pyrimidinyl, or indolyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ ;

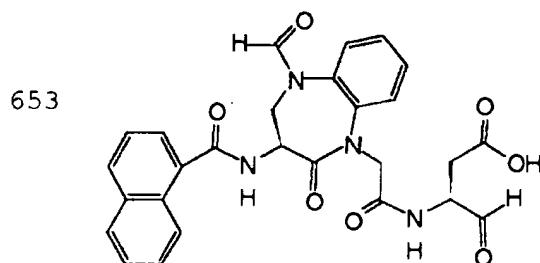
each  $Q_1$  is independently selected from the group consisting of  $-\text{NH}_2$ ,  $-\text{Cl}$ ,  $-\text{F}$ ,  $-\text{Br}$ ,  $-\text{OH}$ ,  $-\text{R}_9$ ,  $-\text{NH}-\text{R}_5$  wherein  $\text{R}_5$  is  $-\text{C}(\text{O})-\text{R}_{10}$  or  $-\text{S}(\text{O})_2-\text{R}_9$ ,  $-\text{OR}_5$  wherein  $\text{R}_5$  is  $-\text{C}(\text{O})-\text{R}_{10}$ ,  $-\text{OR}_9$ ,  $-\text{NHR}_9$ , and

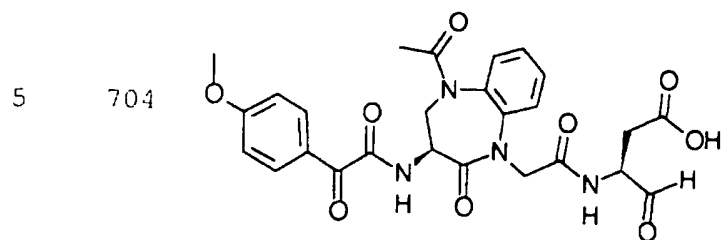
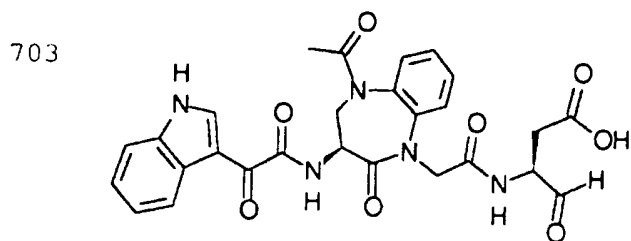
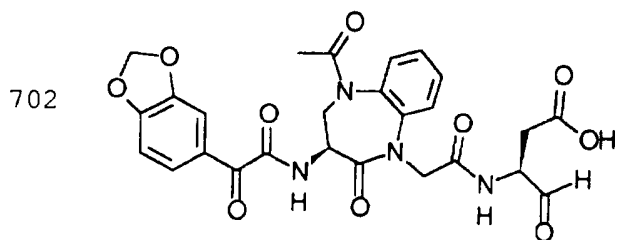
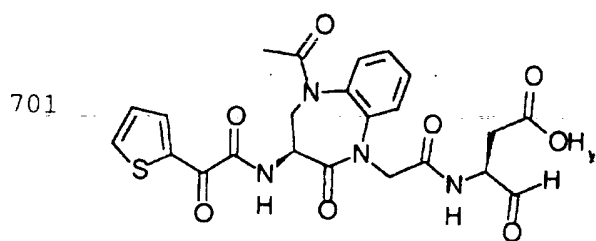


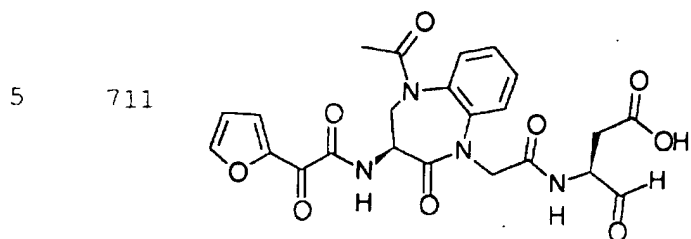
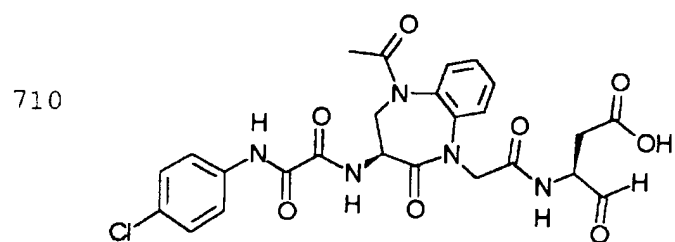
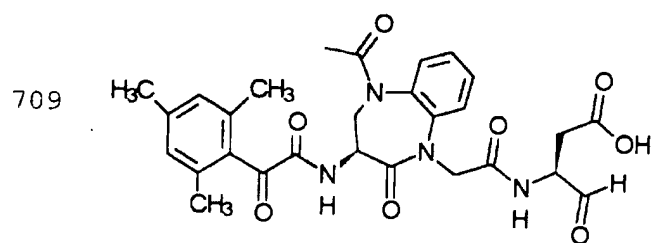
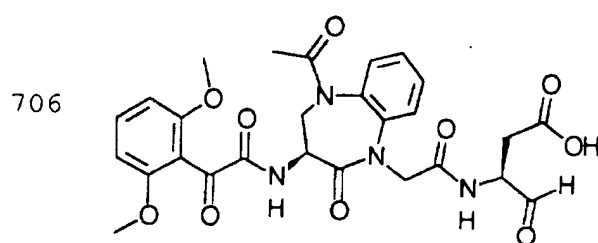
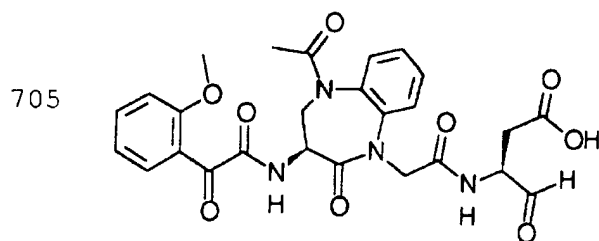
wherein each  $\text{R}_9$  and  $\text{R}_{10}$  are independently a  $-\text{C}_{1-6}$  straight or branched alkyl group optionally substituted with  $-\text{Ar}_3$  wherein  $\text{Ar}_3$  is phenyl;

provided that when  $-\text{Ar}_3$  is substituted with a  $Q_1$  group which comprises one or more additional  $-\text{Ar}_3$  groups, said additional  $-\text{Ar}_3$  groups are not substituted with another  $-\text{Ar}_3$ .

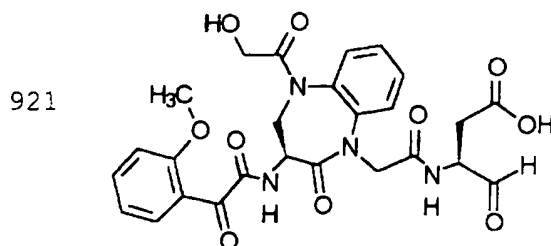
Preferred compounds of this preferred embodiment include, but are not limited to:







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More preferably,  $R_3$  is  $-C(O)-Ar_2$  and the other substituents are as described above.

Alternatively,  $R_3$  is

5  $-C(O)CH_2-T_1-R_{11}$ ;

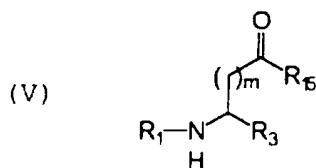
Alternatively,  $R_3$  is  $-C(O)-H$ .

Preferably, in any of the above compounds of embodiment (L),  $R_8$  is selected from the group consisting of:

- 10
- $-C(O)-R_{10}$ ,
  - $-C(O)O-R_9$ ,
  - $-C(O)-CH_2-OR_{10}$ , and
  - $-C(O)-CH_2C(O)-R_9$ .

15 More preferably,  $R_8$  is  $-C(O)-CH_2-OR_{10}$  and  $R_{10}$  is  $-H$  or  $-CH_3$ .

Alternatively, ICE inhibitors of embodiment (L) of this invention are those of formula :



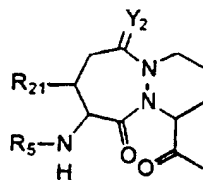
wherein:

20  $m$  is 1;

$R_1$  is:

- 240 -

(e10-B)



R<sub>3</sub> is selected from the group consisting of:

- CN,
- 5        -C(O)-H,
- C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>,
- C(O)-CH<sub>2</sub>-F,
- C=N-O-R<sub>9</sub>, and
- CO-Ar<sub>2</sub>;

10        each R<sub>5</sub> is independently selected from the group consisting of:

- C(O)-R<sub>10</sub>,
- C(O)O-R<sub>9</sub>,
- C(O)-N(R<sub>10</sub>)(R<sub>10</sub>)
- 15        -S(O)<sub>2</sub>-R<sub>9</sub>,
- S(O)<sub>2</sub>-NH-R<sub>10</sub>,
- C(O)-CH<sub>2</sub>-O-R<sub>9</sub>,
- C(O)C(O)-R<sub>10</sub>,
- R<sub>9</sub>,
- 20        -H,
- C(O)C(O)-OR<sub>10</sub>, and
- C(O)C(O)-N(R<sub>9</sub>)(R<sub>10</sub>);

Y<sub>2</sub> is H<sub>2</sub> or O;

25        each T<sub>1</sub> is independently selected from the group consisting of -O- or -S-;

each R<sub>9</sub> is independently selected from the group

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consisting of  $-\text{Ar}_3$  and a  $-\text{C}_{1-6}$  straight or branched alkyl group optionally substituted with  $\text{Ar}_3$ , wherein the  $-\text{C}_{1-6}$  alkyl group is optionally unsaturated;

5 each  $\text{R}_{10}$  is independently selected from the group consisting of  $-\text{H}$ ,  $-\text{Ar}_3$ , a  $\text{C}_{3-6}$  cycloalkyl group, and a  $-\text{C}_{1-6}$  straight or branched alkyl group optionally substituted with  $\text{Ar}_3$ , wherein the  $-\text{C}_{1-6}$  alkyl group is optionally unsaturated;

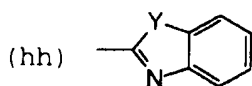
10 each  $\text{R}_{11}$  is independently selected from the group consisting of:

$-\text{Ar}_4$ ,  
 $-(\text{CH}_2)_{1-3}-\text{Ar}_4$ ,  
 $-\text{H}$ , and  
 $-\text{C}(\text{O})-\text{Ar}_4$ ;

15  $\text{R}_{15}$  is selected from the group consisting of  $-\text{OH}$ ,  $-\text{OAr}_3$ ,  $-\text{N}(\text{H})-\text{OH}$ , and  $-\text{OC}_{1-6}$ , wherein  $\text{C}_{1-6}$  is a straight or branched alkyl group optionally substituted with  $-\text{Ar}_3$ ,  $-\text{CONH}_2$ ,  $-\text{OR}_5$ ,  $-\text{OH}$ ,  $-\text{OR}_9$ , or  $-\text{CO}_2\text{H}$ ;

$\text{R}_{21}$  is  $-\text{H}$  or  $-\text{CH}_3$ ;

20  $\text{Ar}_2$  is:



wherein  $\text{Y}$  is  $\text{O}$ ;

25 each  $\text{Ar}_3$  is a cyclic group independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl,

- 242 -

isoxazolyl, benzotriazolyl, benzimidazolyl,  
 thienothienyl, imidazolyl, thiadiazolyl,  
 benzo[b]thiophenyl, pyridyl benzofuranyl, and indolyl,  
 and said cyclic group optionally being singly or  
 5 multiply substituted by  $-Q_1$ ;

each  $Ar_4$  is a cyclic group independently selected  
 from the set consisting of phenyl, tetrazolyl,  
 pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and  
 thienyl, and said cyclic group optionally being singly  
 10 or multiply substituted by  $-Q_1$ ;

each  $Q_1$  is independently selected from the group  
 consisting of  $-NH_2$ ,  $-Cl$ ,  $-F$ ,  $-Br$ ,  $-OH$ ,  $-R_9$ ,  $-NH-R_5$   
 wherein  $R_5$  is  $-C(O)-R_{10}$  or  $-S(O)_2-R_9$ ,  $-OR_5$  wherein  $R_5$  is  
 $-C(O)-R_{10}$ ,  $-OR_9$ ,  $-NHR_9$ , and



20 provided that when  $-Ar_3$  is substituted with a  $Q_1$   
 group which comprises one or more additional  $-Ar_3$   
 groups, said additional  $-Ar_3$  groups are not substituted  
 with another  $-Ar_3$ ;

provided that when:

25 m is 1;  
 $R_{15}$  is  $-OH$ ;  
 $R_{21}$  is  $-H$ ; and

$Y_2$  is O and  $R_3$  is  $-C(O)-H$ , then  $R_5$  cannot be:  
 $-C(O)-R_{10}$ , wherein  $R_{10}$  is  $-Ar_3$  and the  $Ar_3$  cyclic



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group is phenyl, unsubstituted by  $-Q_1$ , 4-(carboxymethoxy)phenyl, 2-fluorophenyl, 2-pyridyl, N-(4-methylpiperazino)methylphenyl, or

5  $-C(O)-OR_9$ , wherein  $R_9$  is  $-CH_2-Ar_3$ , and the  $Ar_3$  cyclic group is phenyl, unsubstituted by  $-Q_1$ ; and when

$Y_2$  is O,  $R_3$  is  $-C(O)-CH_2-T_1-R_{11}$ ,  $T_1$  is O, and  $R_{11}$  is  $Ar_4$ , wherein the  $Ar_4$  cyclic group is 5-(1-(4-chlorophenyl)-3-trifluoromethyl)pyrazolyl), then  $R_5$  cannot be:

10  $-H$ ;

$-C(O)-R_{10}$ , wherein  $R_{10}$  is  $-Ar_3$  and the  $Ar_3$  cyclic group is 4-(dimethylaminomethyl)phenyl, phenyl, 4-(carboxymethylthio)phenyl, 4-(carboxyethylthio)phenyl, 4-(carboxyethyl)phenyl, 4-(carboxypropyl)phenyl, 2-fluorophenyl, 2-pyridyl, N-(4-methylpiperazino)methylphenyl, or

15  $-C(O)-OR_9$ , wherein  $R_9$  is isobutyl or  $-CH_2-Ar_3$  and the  $Ar_3$  cyclic group is phenyl;

and when  $R_{11}$  is  $Ar_4$ , wherein the  $Ar_4$  cyclic group is 5-(1-phenyl-3-trifluoromethyl)pyrazolyl or 5-(1-(4-chloro-2-pyridinyl)-3-trifluoromethyl)pyrazolyl, then  $R_5$  cannot be:

20  $-C(O)-OR_9$ , wherein  $R_9$  is  $-CH_2-Ar_3$ , and the  $Ar_3$  cyclic group is phenyl;

25 and when  $R_{11}$  is  $Ar_4$ , wherein the  $Ar_4$  cyclic group is 5-(1-(2-pyridyl)-3-trifluoromethyl)pyrazolyl), then  $R_5$  cannot be:

$-C(O)-R_{10}$ , wherein  $R_{10}$  is  $-Ar_3$  and the  $Ar_3$  cyclic group is 4-(dimethylaminomethyl)phenyl, or

30  $-C(O)-OR_9$ , wherein  $R_9$  is  $-CH_2-Ar_3$ , and the  $Ar_3$  cyclic group is phenyl, unsubstituted by  $-Q_1$ ; and when

- 244 -

Y<sub>2</sub> is O, R<sub>3</sub> is -C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>, T<sub>1</sub> is O, and R<sub>11</sub> is -C(O)-Ar<sub>4</sub>, wherein the Ar<sub>4</sub> cyclic group is 2,5-dichlorophenyl, then R<sub>5</sub> cannot be:

5 -C(O)-R<sub>10</sub>, wherein R<sub>10</sub> is -Ar<sub>3</sub> and the Ar<sub>3</sub> cyclic group is 4-(dimethylaminomethyl)phenyl, 4-(N-morpholinomethyl)phenyl, 4-(N-methylpiperazinomethyl)phenyl, 4-(N-(2-methylimidazolylmethyl)phenyl, 5-benzimidazolyl, 5-benzotriazolyl, N-carboethoxy-5-benzotriazolyl, N-  
10 carboethoxy-5-benzimidazolyl, or

-C(O)-OR<sub>9</sub>, wherein R<sub>9</sub> is -CH<sub>2</sub>-Ar<sub>3</sub>, and the Ar<sub>3</sub> cyclic group is phenyl, unsubstituted by -Q<sub>1</sub>; and when

Y<sub>2</sub> is H<sub>2</sub>, R<sub>3</sub> is -C(O)-CH<sub>2</sub>-T<sub>1</sub>-R<sub>11</sub>, T<sub>1</sub> is O, and R<sub>11</sub> is -C(O)-Ar<sub>4</sub>, wherein the Ar<sub>4</sub> cyclic group is 2,5-dichlorophenyl, then R<sub>5</sub> cannot be:

15 -C(O)-OR<sub>9</sub>, wherein R<sub>9</sub> is -CH<sub>2</sub>-Ar<sub>3</sub> and the Ar<sub>3</sub> cyclic group is phenyl.

Preferably, in any of the above compounds of embodiment (L), R<sub>3</sub> is -C(O)-H and R<sub>5</sub> is -C(O)-R<sub>10</sub> or  
20 -C(O)-C(O)-R<sub>10</sub> and the other substituents are as defined above.

More preferably R<sub>10</sub> is -Ar<sub>3</sub> and the other substituents are as defined above.

25 More preferably in these more preferred compounds:

R<sub>5</sub> is -C(O)-R<sub>10</sub> and R<sub>10</sub> is Ar<sub>3</sub>, wherein the Ar<sub>3</sub> cyclic group is phenyl optionally being singly or multiply substituted by:

30 -R<sub>9</sub>, wherein R<sub>9</sub> is a C<sub>1-4</sub> straight or branched alkyl group;

-F,

-Cl,

-N(H)-R<sub>5</sub>, wherein -R<sub>5</sub> is -H or -C(O)-R<sub>10</sub>,

- 245 -

wherein  $R_{10}$  is a  $-C_{1-6}$  straight or branched alkyl group optionally substituted with  $Ar_3$ , wherein  $Ar_3$  is phenyl,

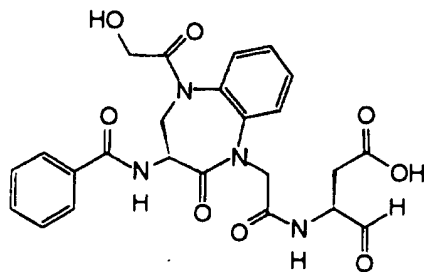
5  $-N(R_9)(R_{10})$ , wherein  $R_9$  and  $R_{10}$  are independently a  $-C_{1-4}$  straight or branched alkyl group, or

$-O-R_5$ , wherein  $R_5$  is H or a  $-C_{1-4}$  straight or branched alkyl group.

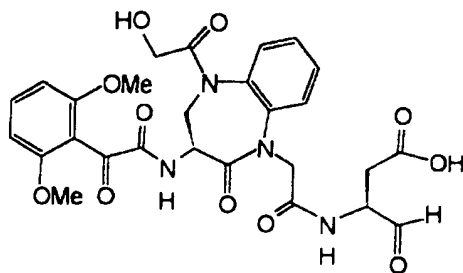
Preferred compounds of this preferred embodiment include, but are not limited to:

10

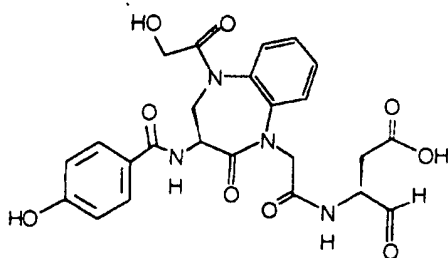
668



678

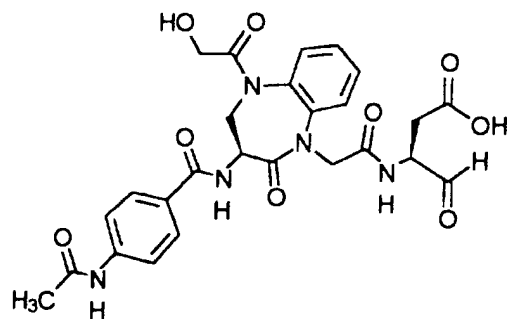


691b



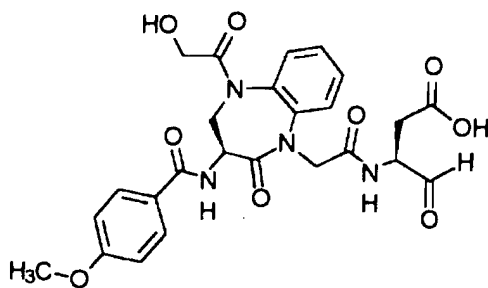
- 246 -

911



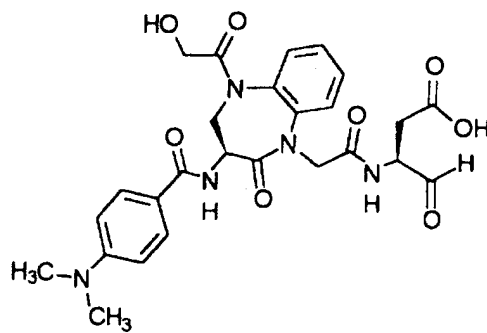
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912



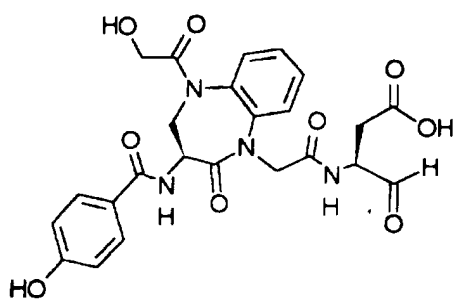
;

913



; and

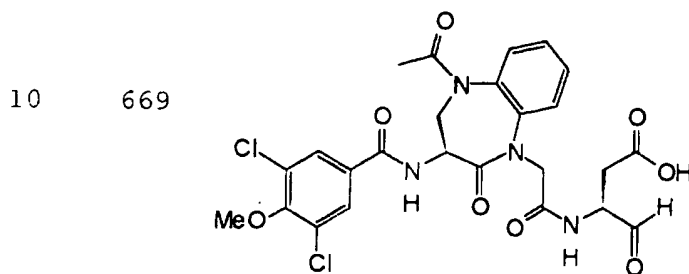
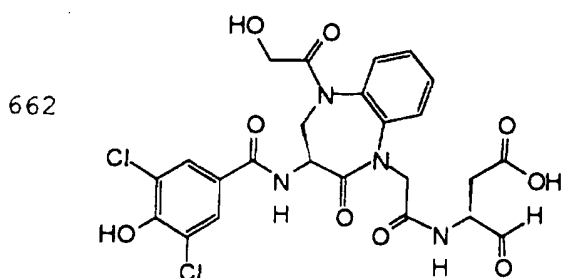
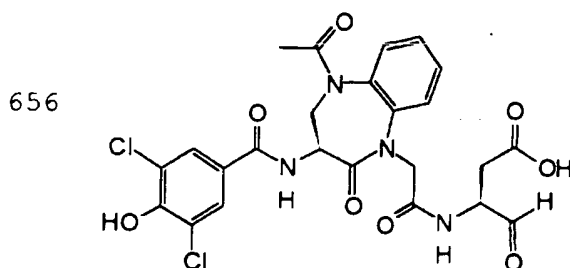
916



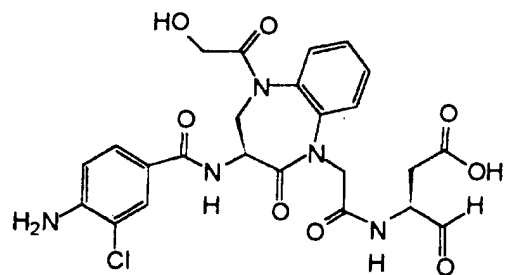
Most preferably, Ar<sub>3</sub> is phenyl being singly or multiply substituted at the 3- or 5-position by -Cl or at the 4-position by -NH-R<sub>5</sub>, -N(R<sub>9</sub>)(R<sub>10</sub>), or -O-R<sub>5</sub>.

5

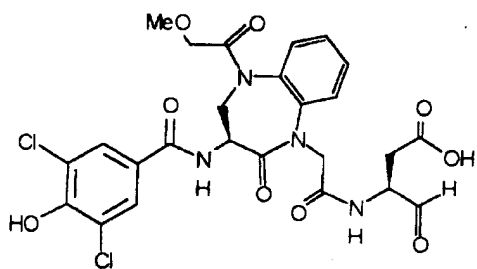
Preferred compounds of this most preferred embodiment include, but are not limited to:



686

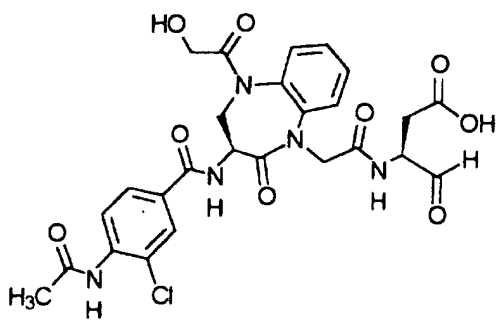


689a

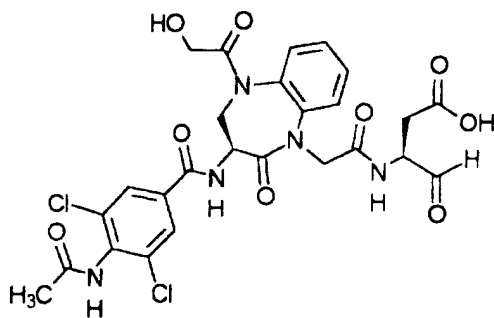


1

914



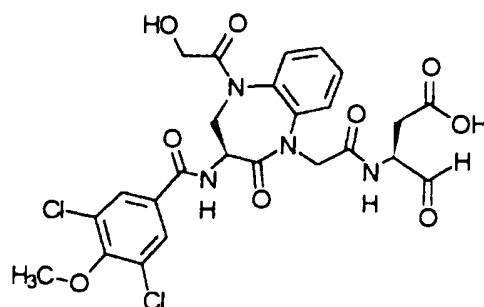
915



; and

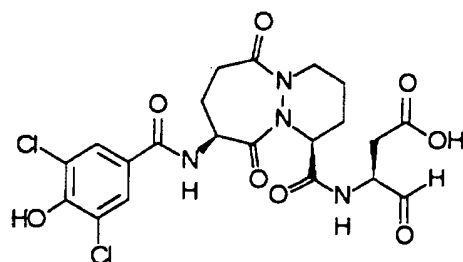
- 249 -

918



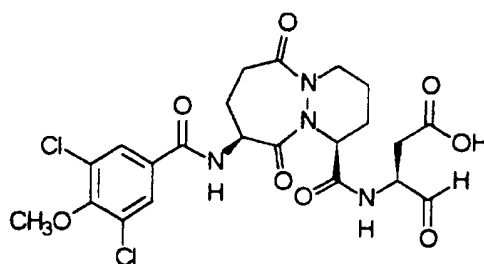
Other preferred compounds of this most preferred embodiment include, but are not limited to:

5      214k



; and

214m

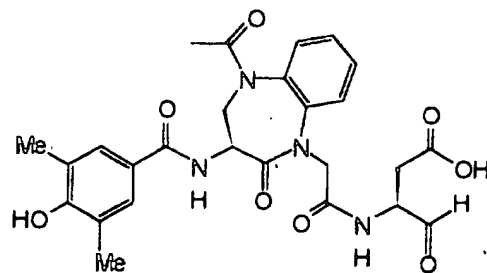


Alternatively, Ar<sub>3</sub> is phenyl being singly or multiply substituted at the 3- or 5-position by -R<sub>9</sub>, wherein R<sub>9</sub> is a C<sub>1-4</sub> straight or branched alkyl group; and at the 4-position by -O-R<sub>6</sub>.

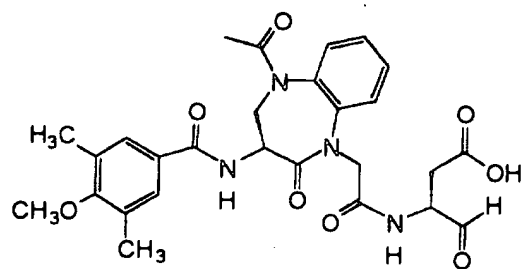
Preferred compounds of this most preferred embodiment include, but are not limited to:

- 250 -

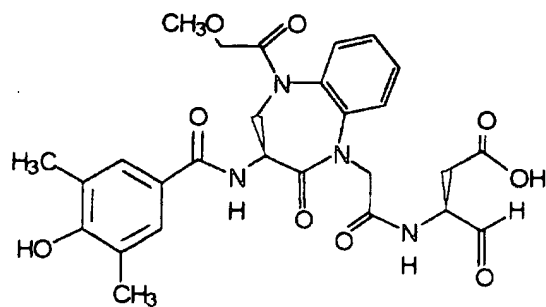
671



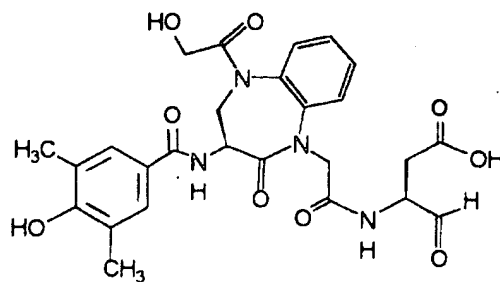
684



689b



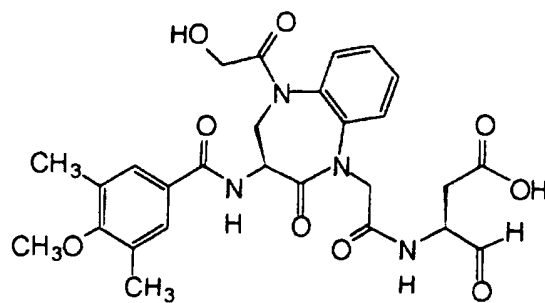
691a





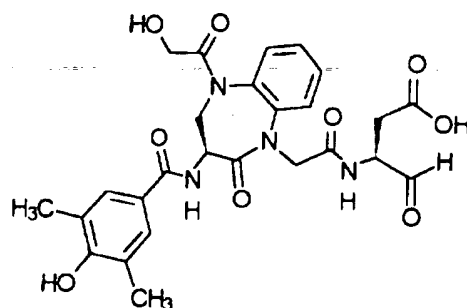
- 251 -

694



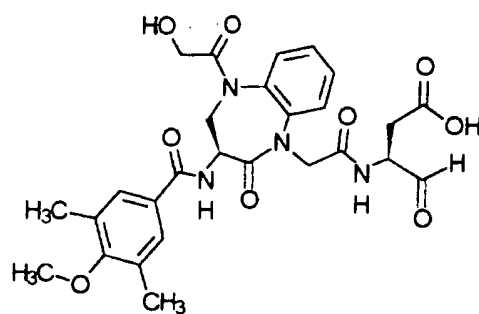
;

917



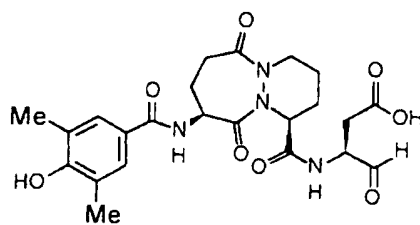
; and

922



Another preferred compound of  
 5 this most preferred embodiment includes, but is not  
 limited to:

214w

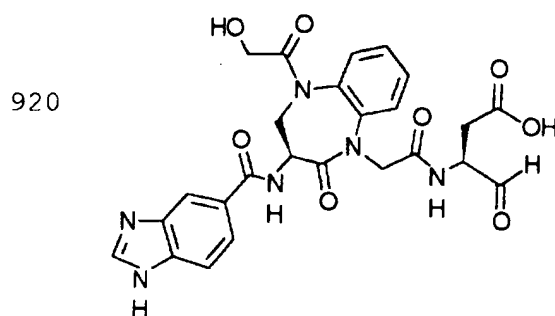
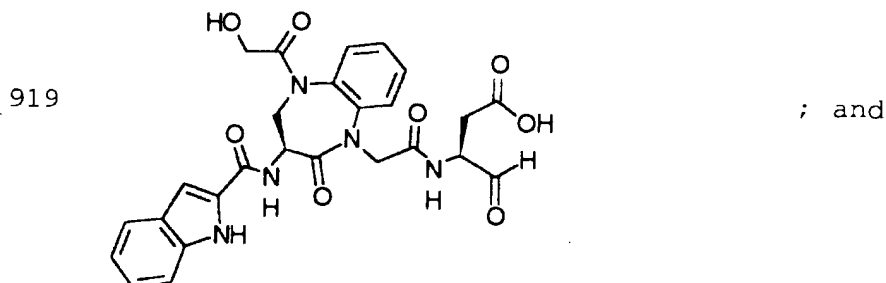


- 252 -

Alternatively, in this more preferred embodiment:

$R_5$  is  $-C(O)-R_{10}$ , wherein  $R_{10}$  is  $Ar_3$  and the  $Ar_3$  cyclic group is selected from the group consisting of  
 5 is indolyl, benzimidazolyl, thienyl, quinolyl, isoquinolyl and benzo[b]thiophenyl, and said cyclic group optionally being singly or multiply substituted by  $-Q_1$ .

Preferred compounds of this more  
 10 preferred embodiment include, but are not limited to:

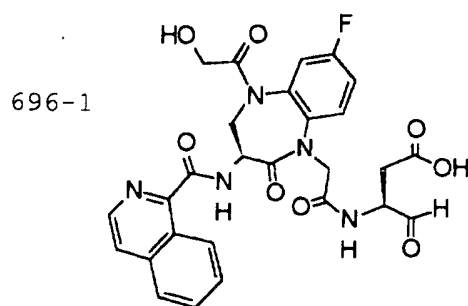
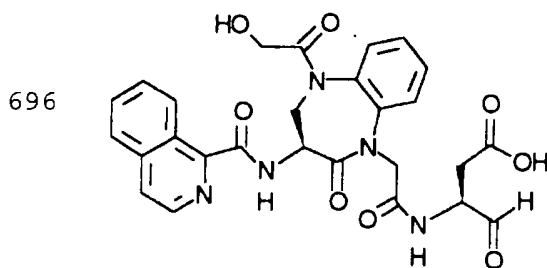


Most preferably, the  $Ar_3$  cyclic group is isoquinolyl, and said cyclic group optionally  
 15 being singly or multiply substituted by  $-Q_1$ .

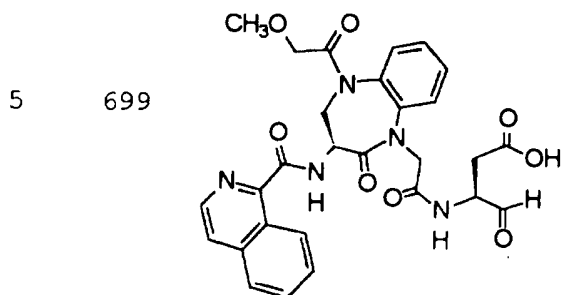
A preferred compound of this most preferred embodiment includes, but is not limited

- 253 -

to:

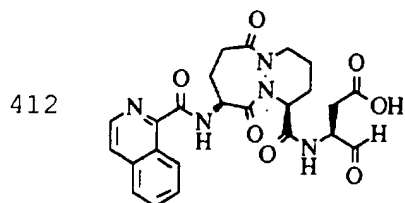


; and



Another preferred compound of this most preferred embodiment includes, but is not limited to:

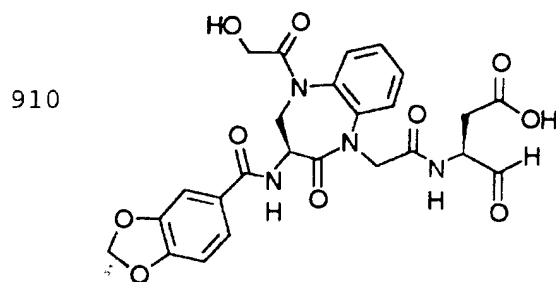
- 254 -



Alternatively, in this more preferred  
embodiment  $R_5$  is  $-C(O)-R_{10}$ , wherein  $R_{10}$  is  $-Ar_3$  and the  
5  $Ar_3$  cyclic group is phenyl, substituted by



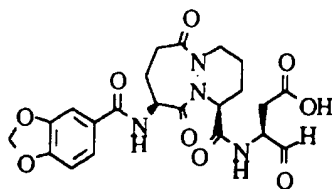
A preferred compound of this more  
preferred embodiment includes, but is not limited to:



15 A preferred compound of this more  
preferred embodiment includes, but is not limited to:

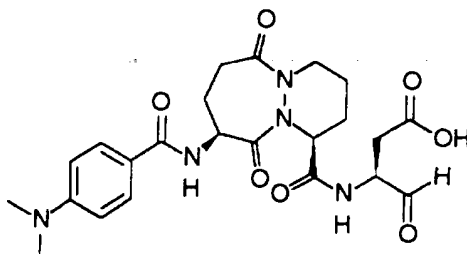
- 255 -

415



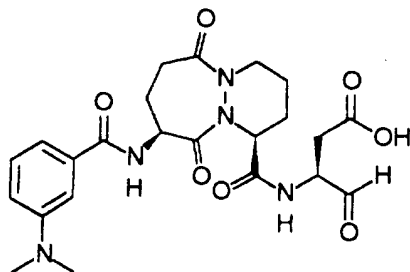
Other compounds of embodiment (L) include,  
but are not limited to:

214f

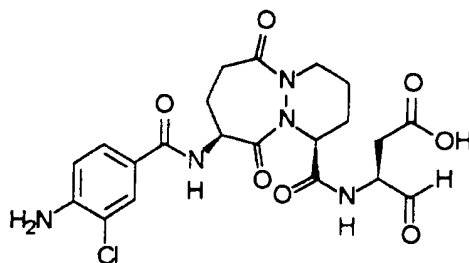


5

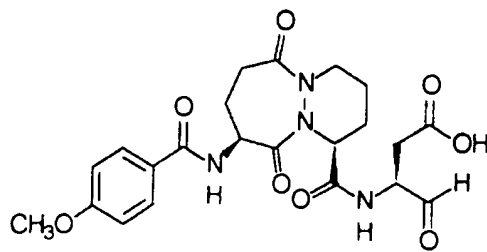
214g



214h

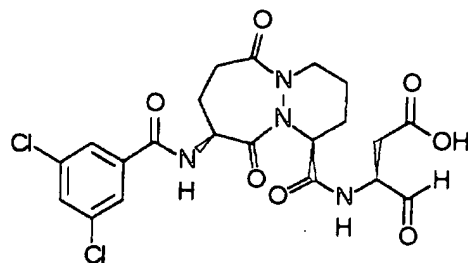


214i

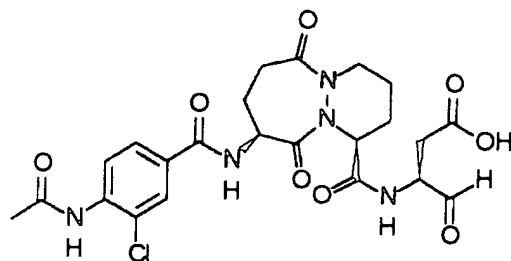


- 256 -

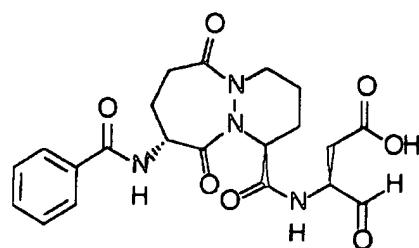
214j



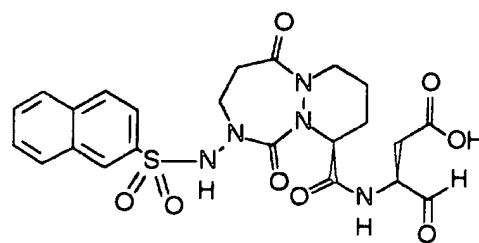
214l



246b

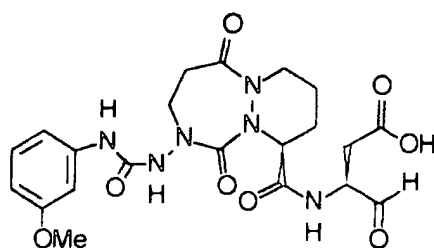


265a



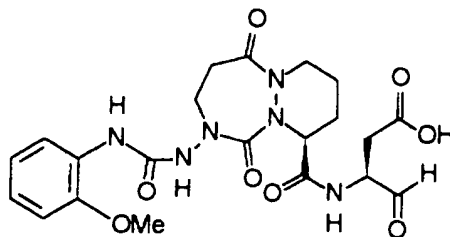
5

265c

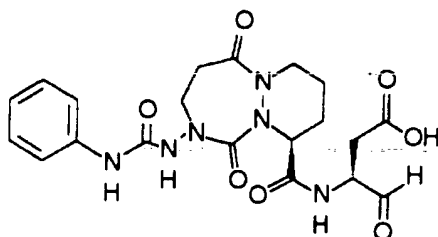


- 257 -

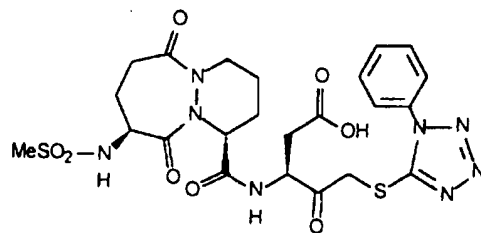
265d



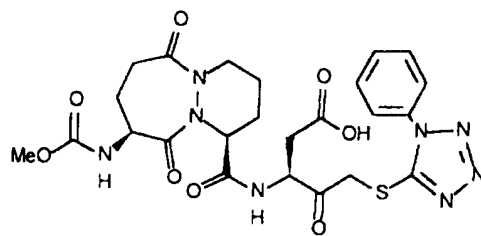
265f



280b

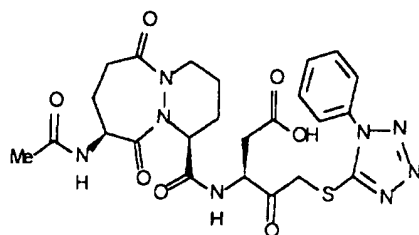


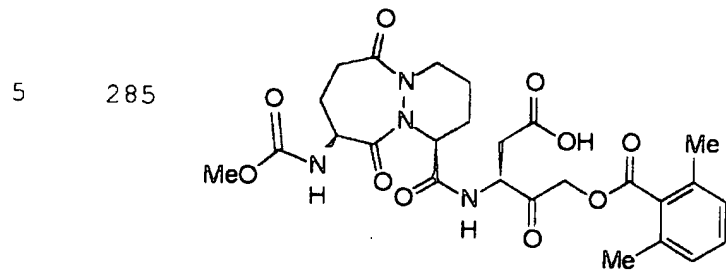
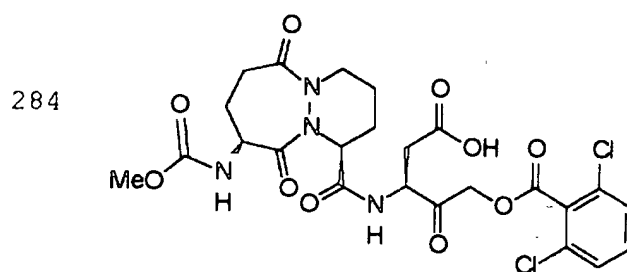
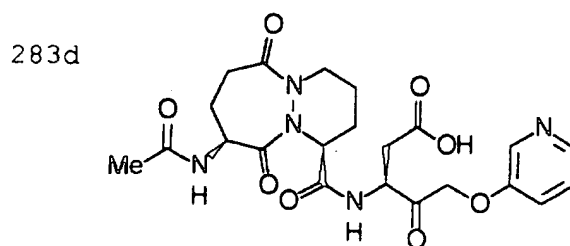
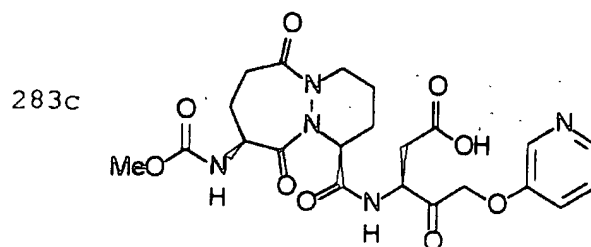
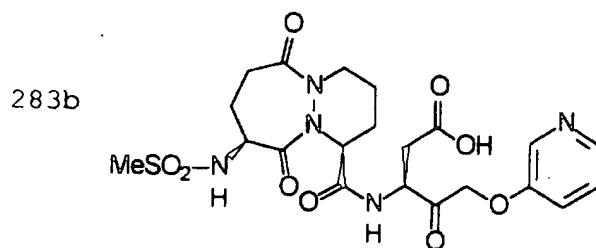
280c



5

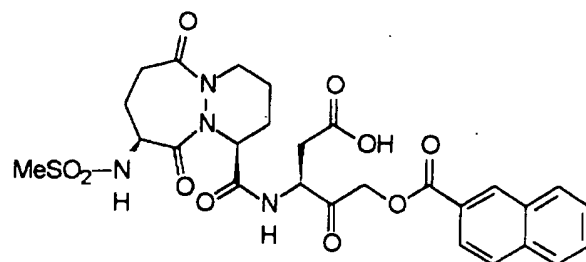
280d



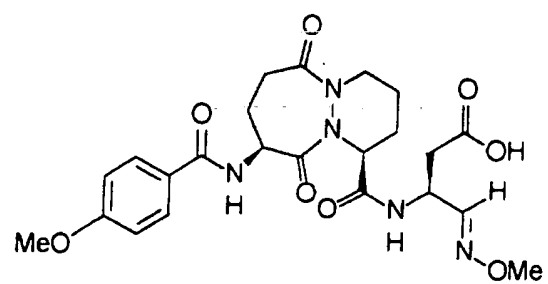




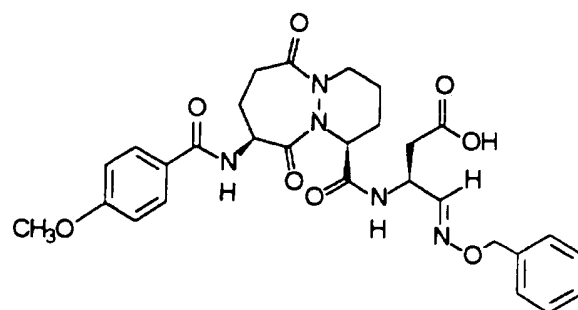
286



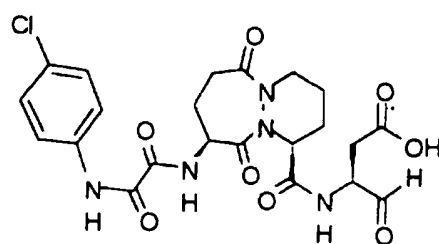
30.8c



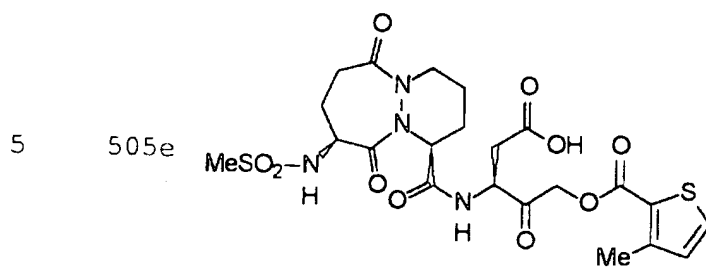
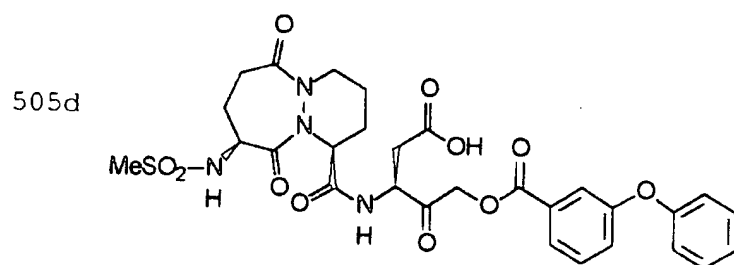
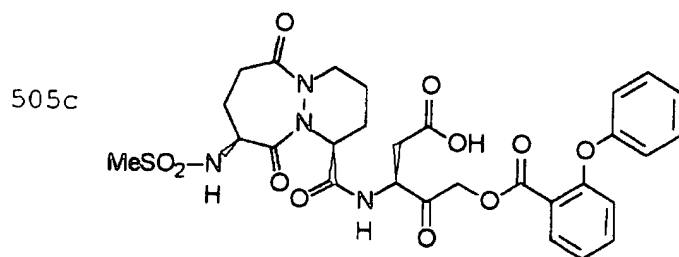
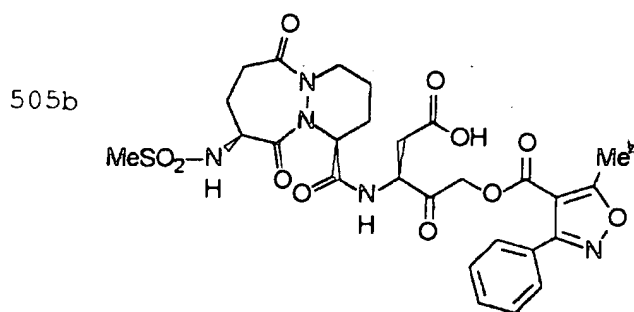
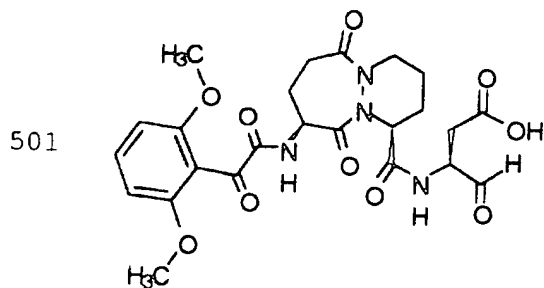
308d



500

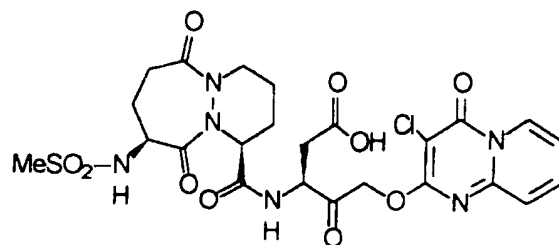


- 260 -

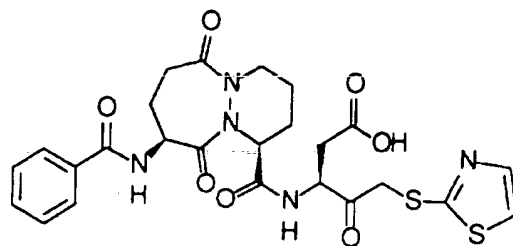


- 261 -

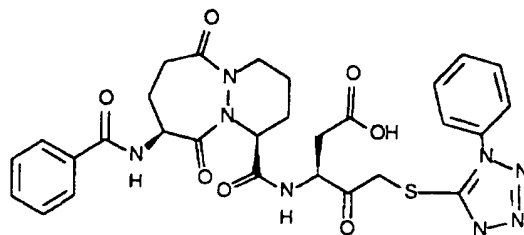
505f



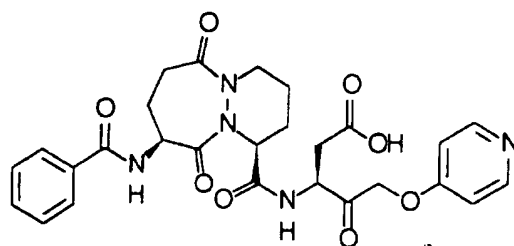
510a



510b

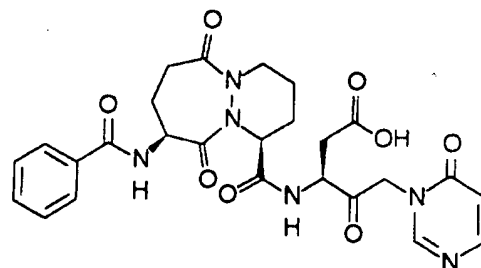


510c



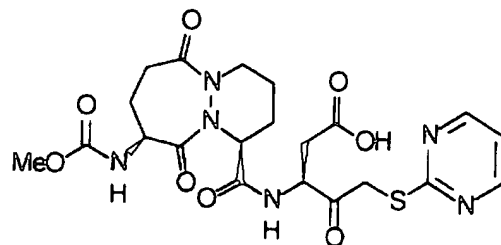
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510d

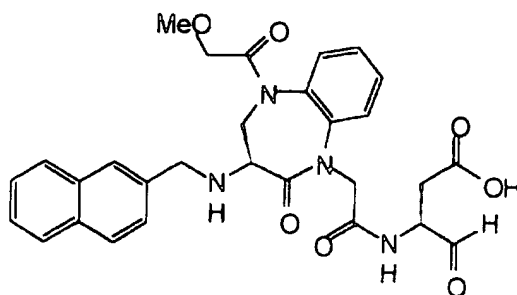


- 262 -

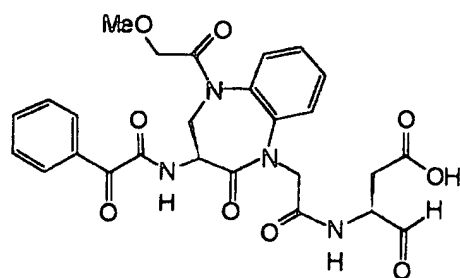
511c



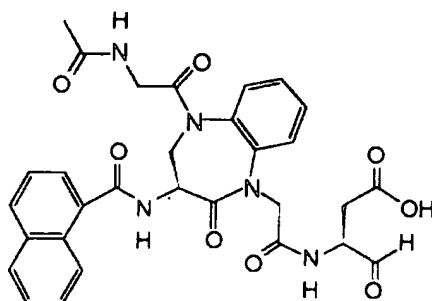
640



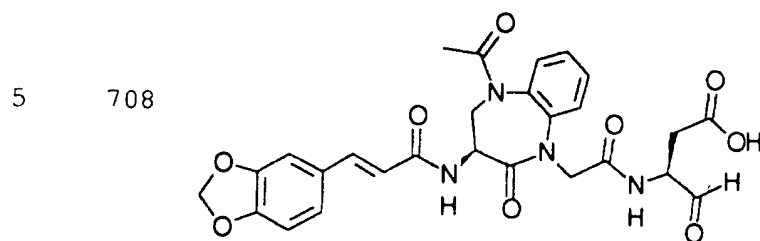
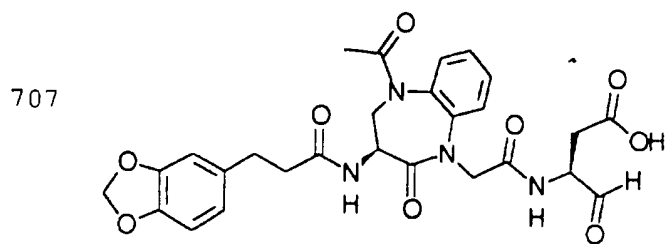
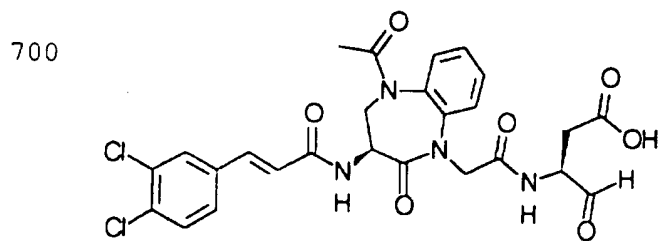
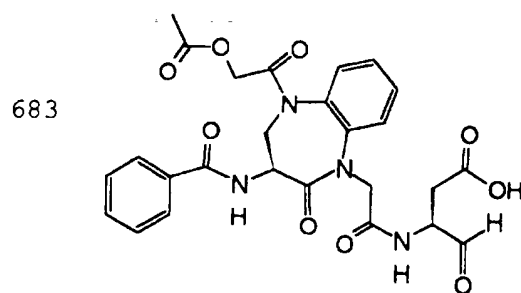
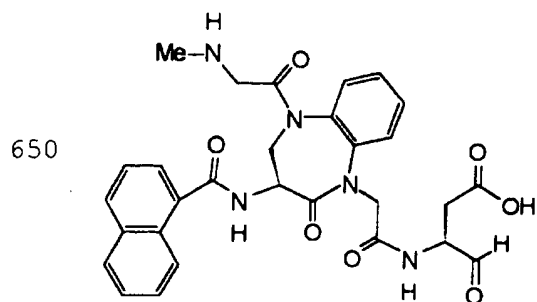
642



645

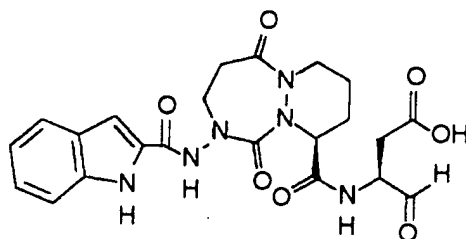


- 263 -



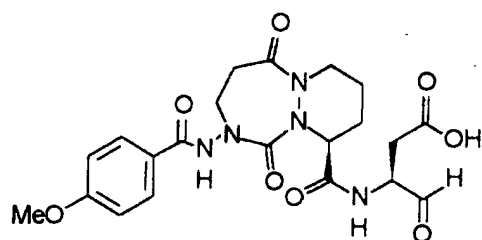
- 264 -

1018



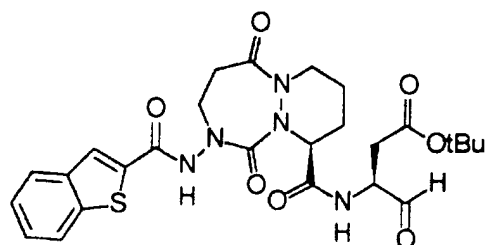
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1052



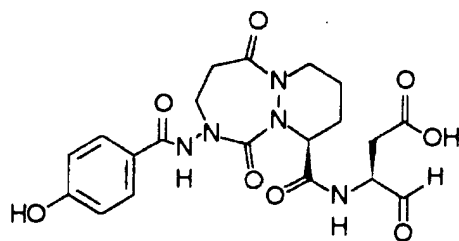
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1053



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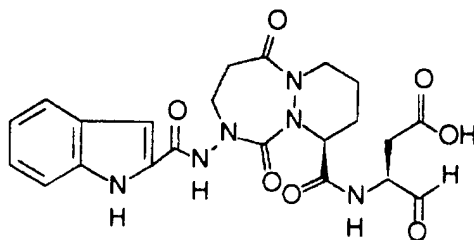
1056



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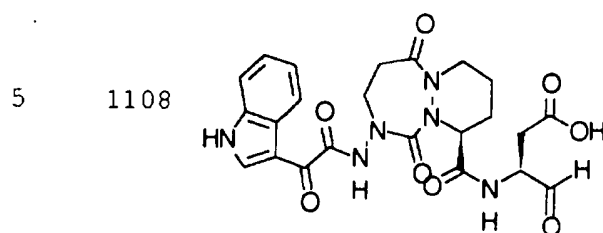
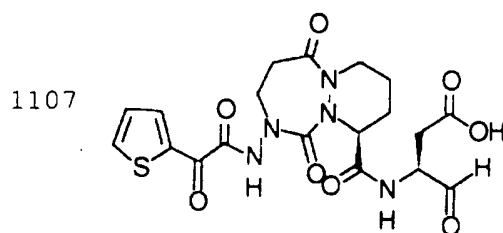
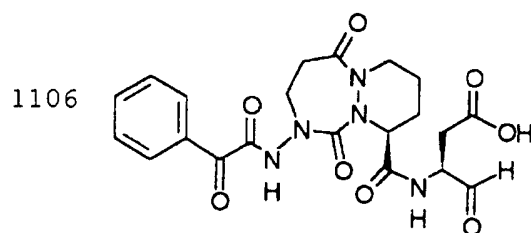
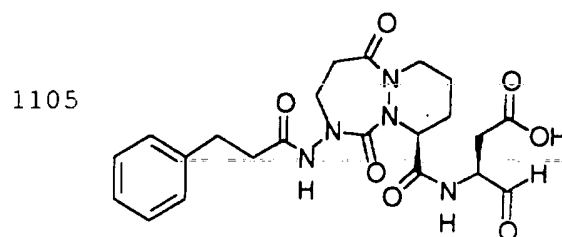
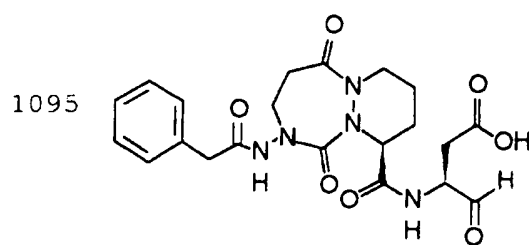
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1075



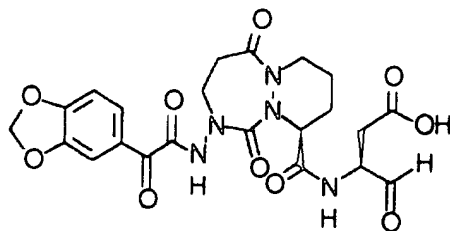
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- 265 -

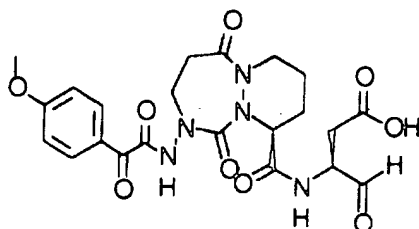


- 266 -

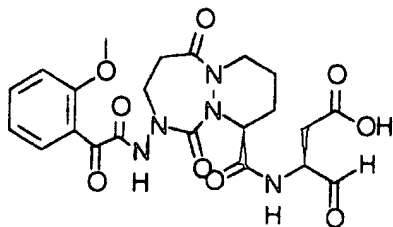
1109



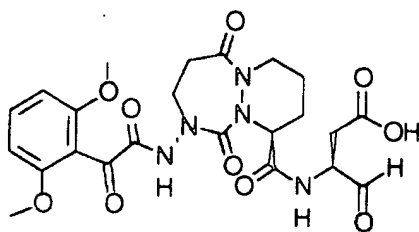
1110



1111

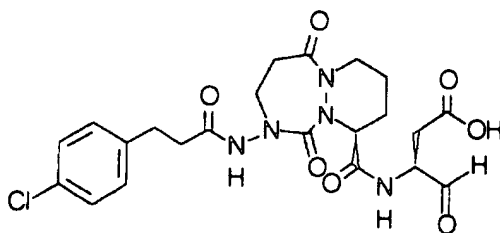


1112



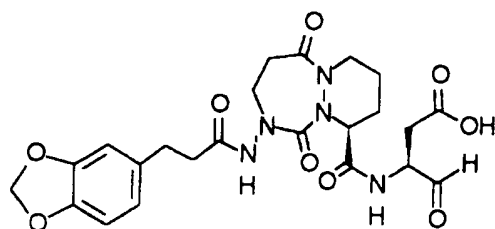
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1113

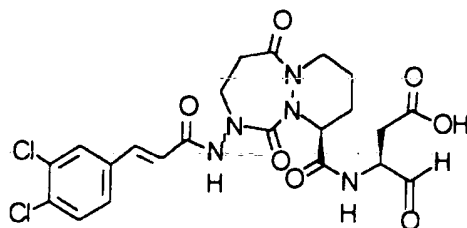




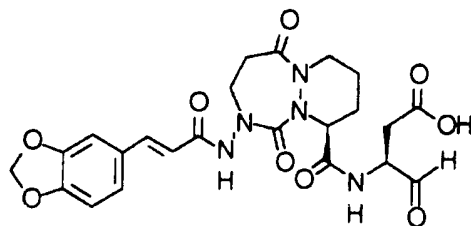
1114



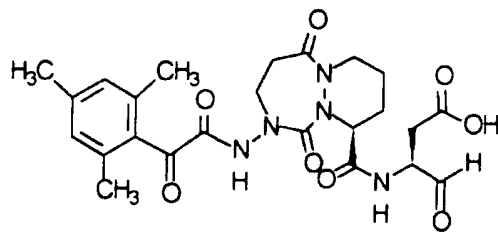
1115



1116

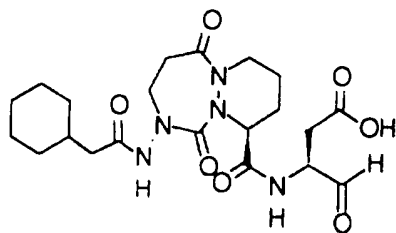


1117

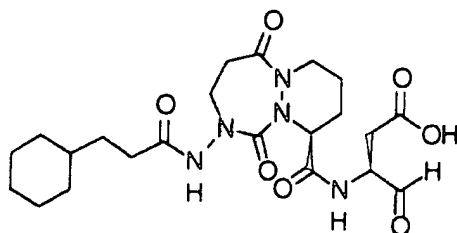


5

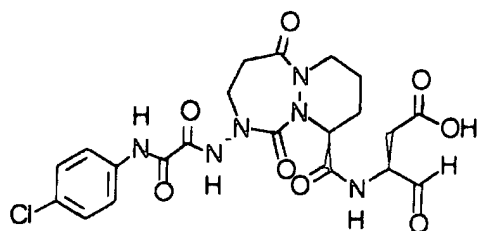
1118



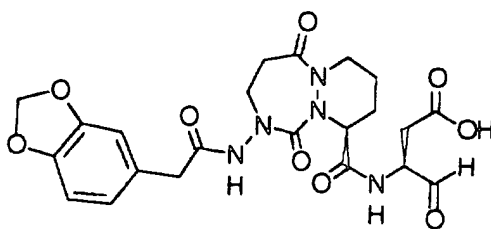
1119



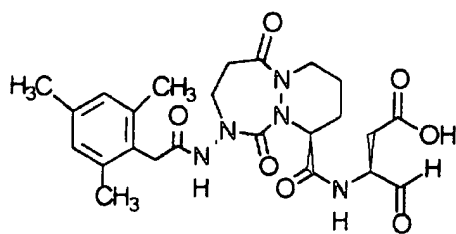
1120



1121

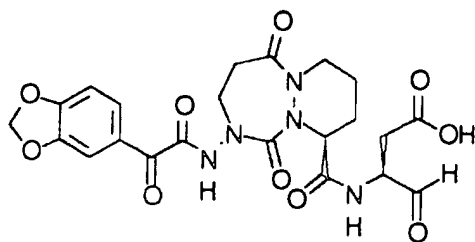


1122

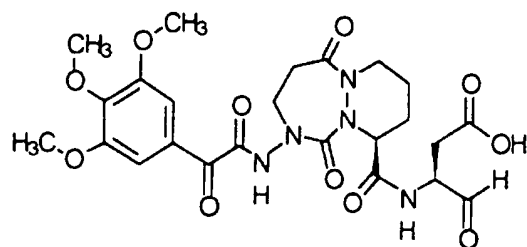


5

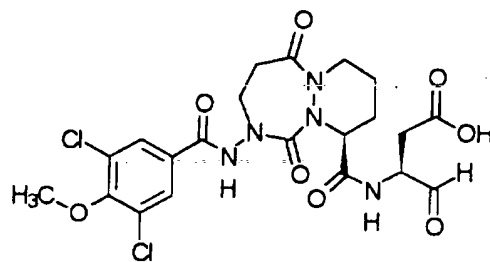
1123



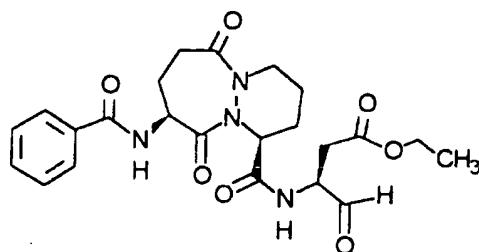
1124



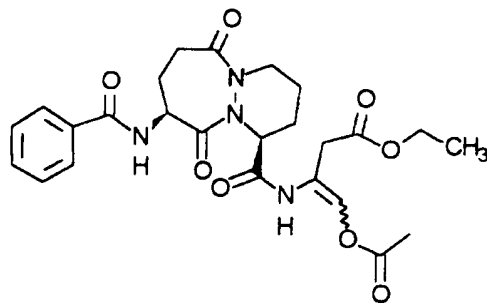
1125



2100i



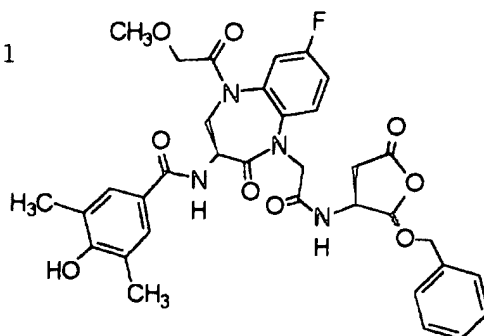
5

$$2100j$$


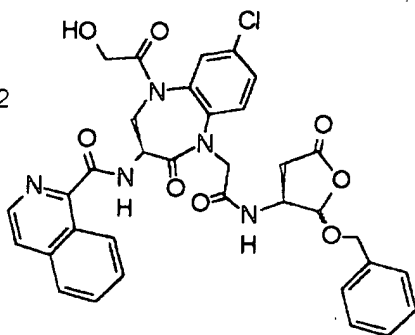
Other compounds of embodiment (K) include, but are not limited to:

- 270 -

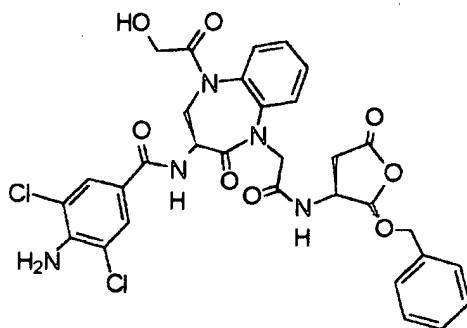
688b-1



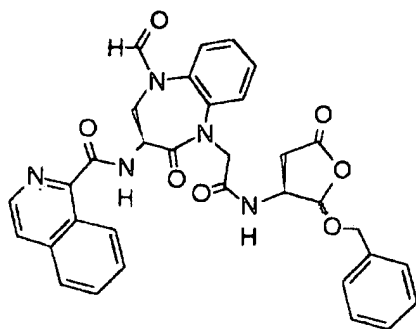
696a-2



5 697a

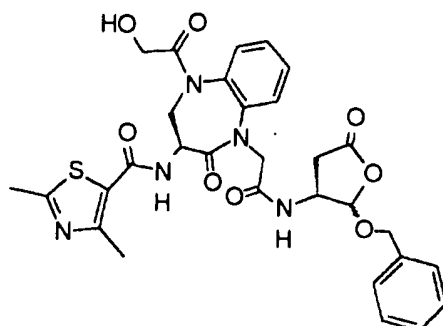


698a



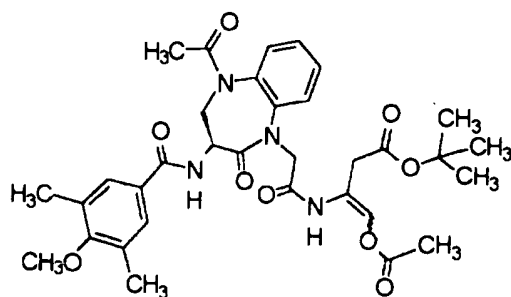
- 271 -

800

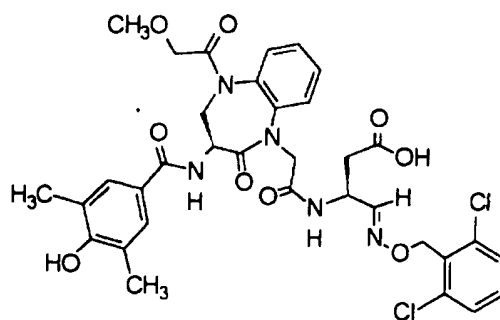


Other compounds of embodiment (L) include,  
but are not limited to:

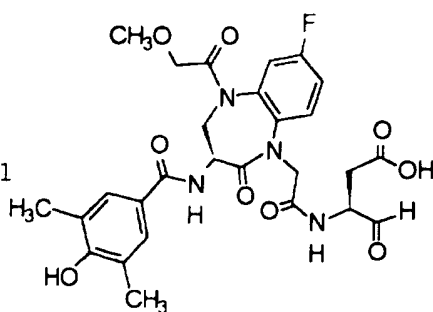
5 684a



688c

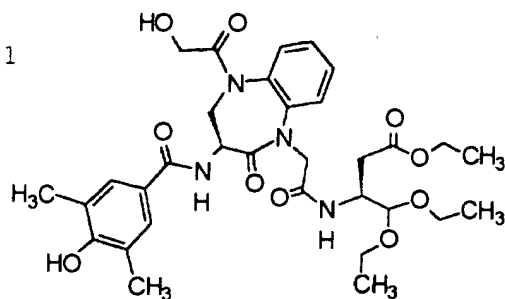


689b-1

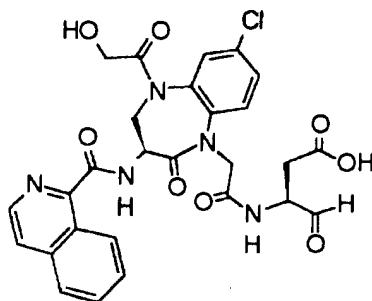


- 272 -

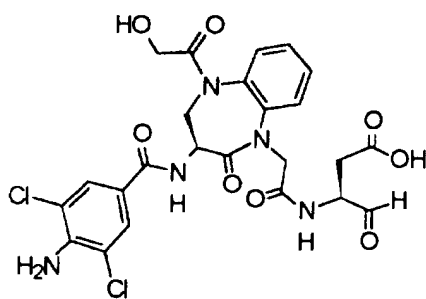
690a-1



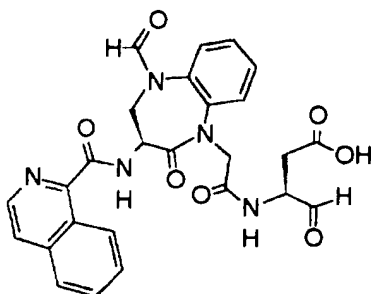
696-2



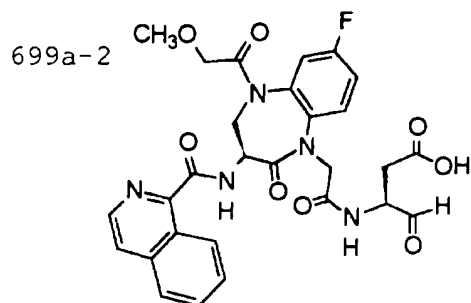
5 697



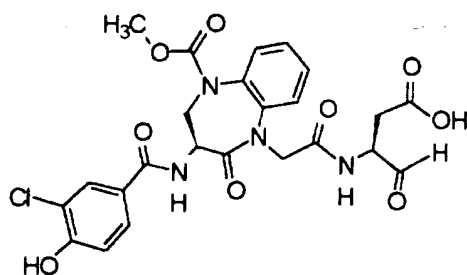
698



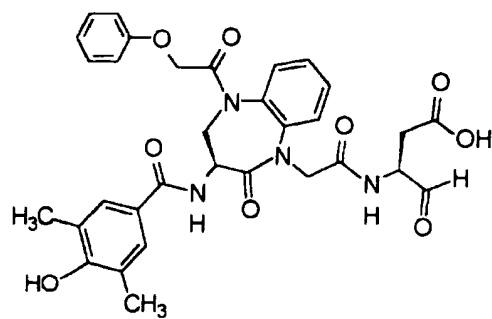
- 273 -



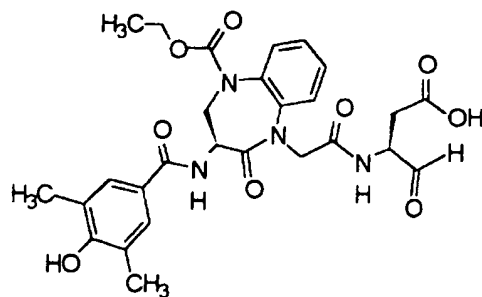
720



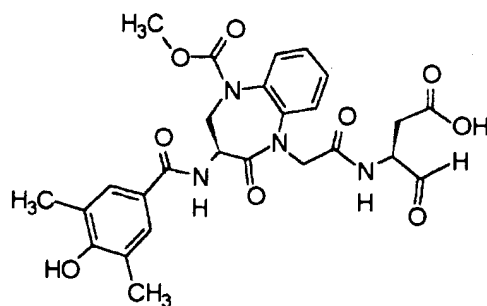
5 721



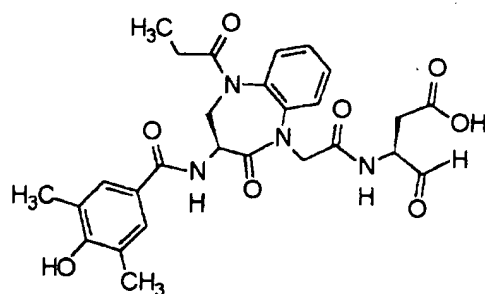
722



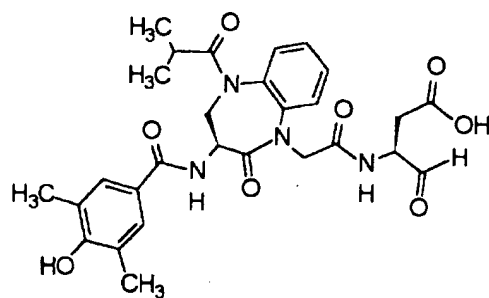
723



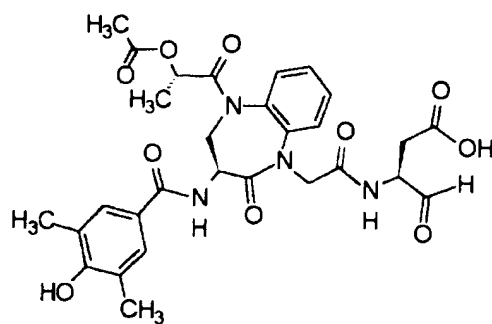
724



5            725



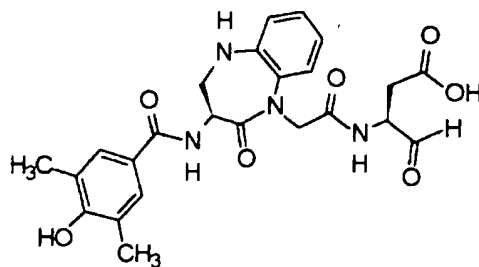
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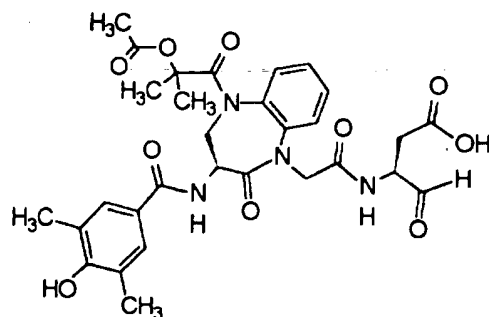


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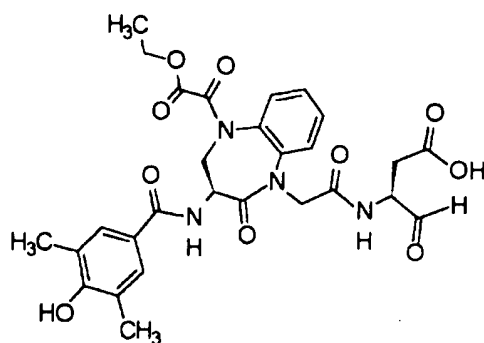


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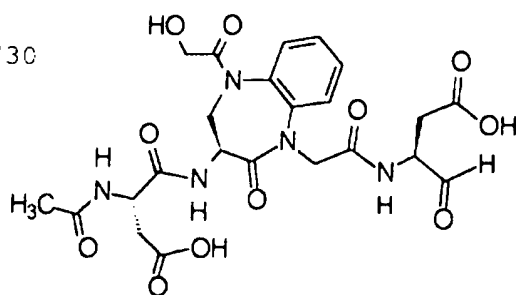


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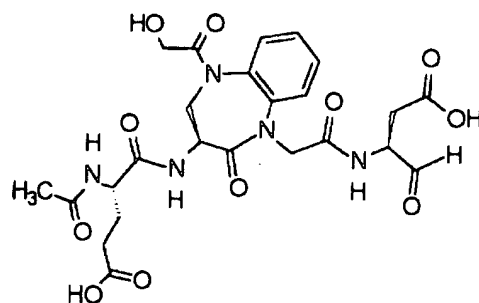


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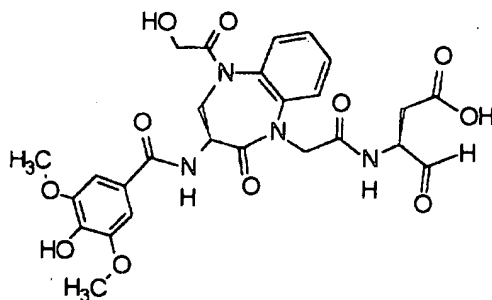


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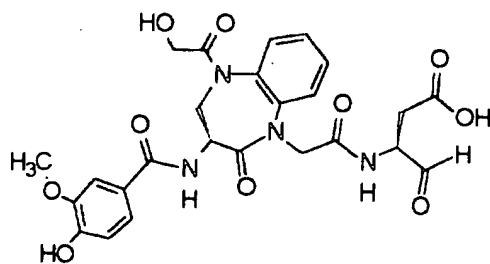
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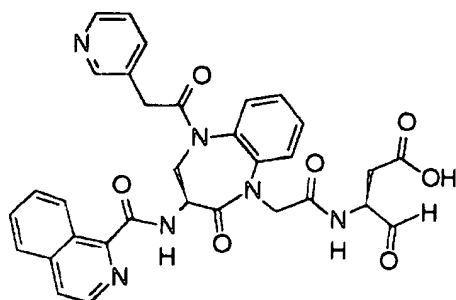
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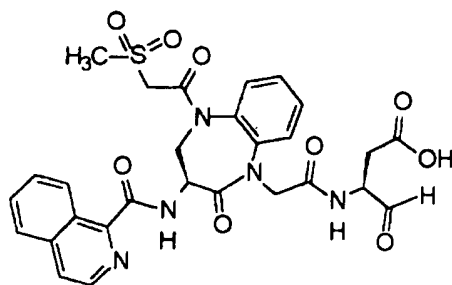


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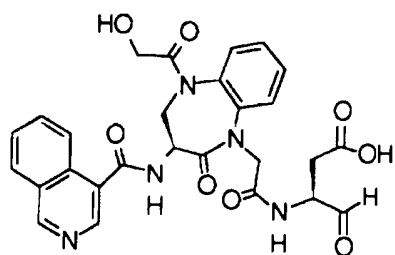


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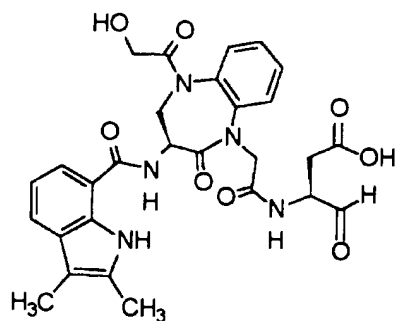
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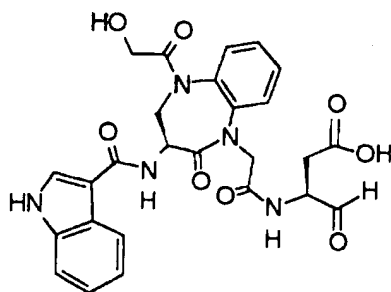
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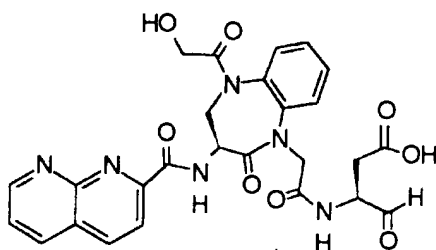
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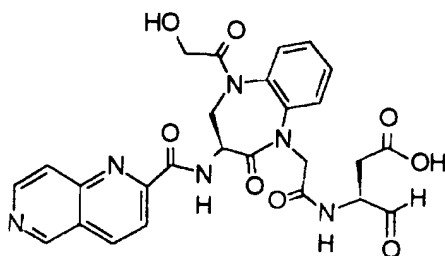
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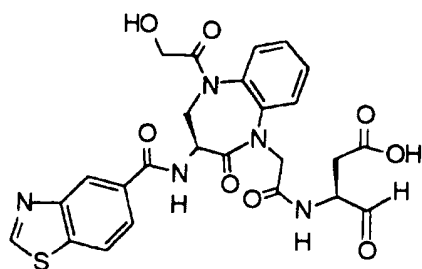


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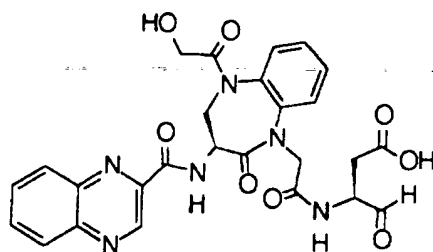


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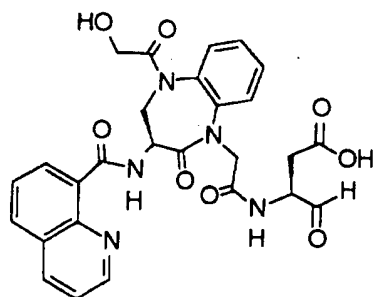
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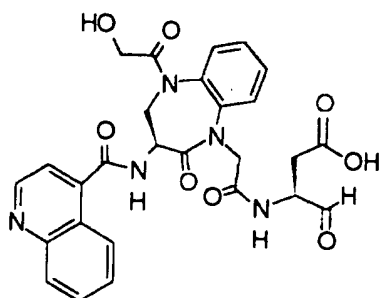
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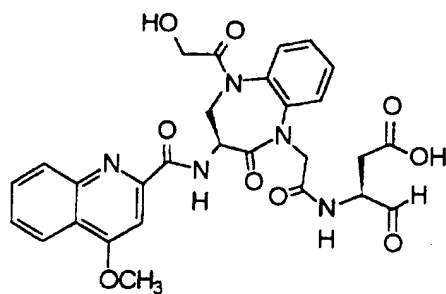


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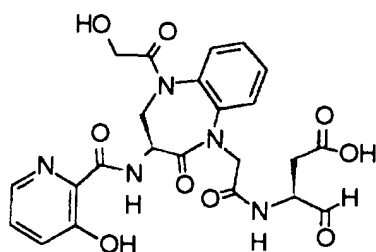


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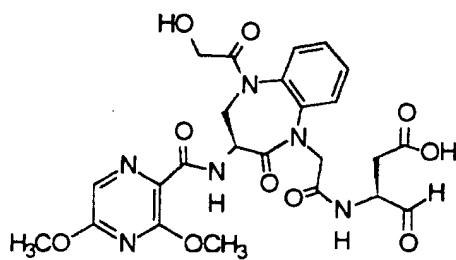
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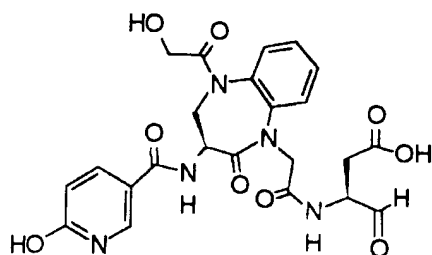
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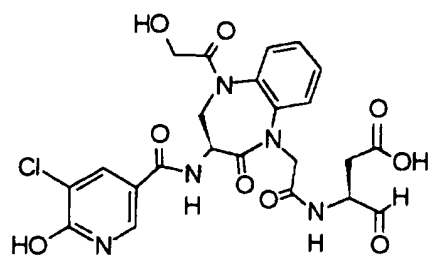
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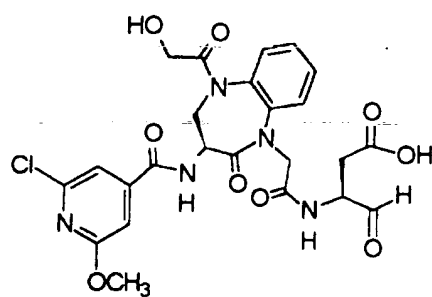
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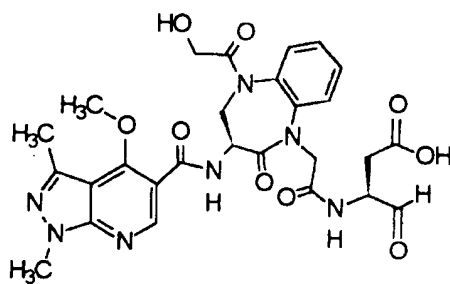
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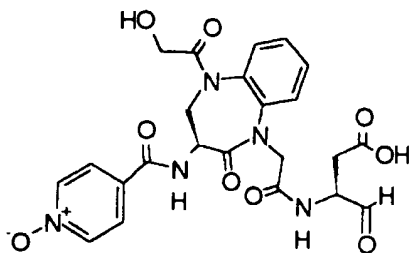
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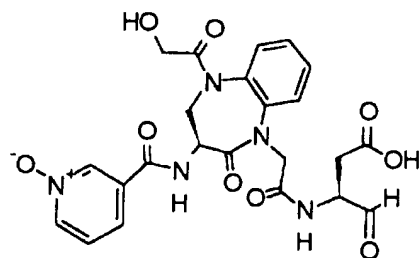


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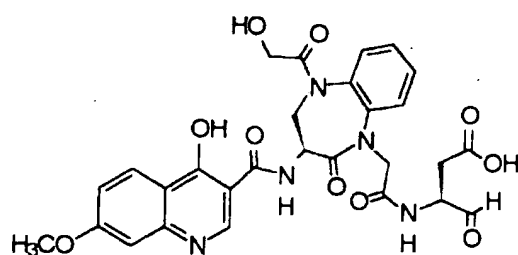


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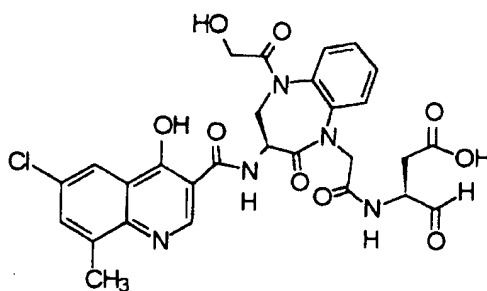
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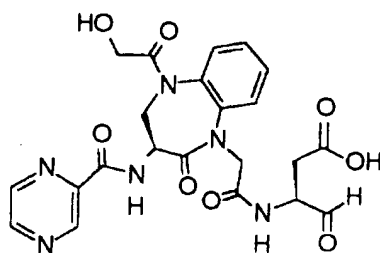
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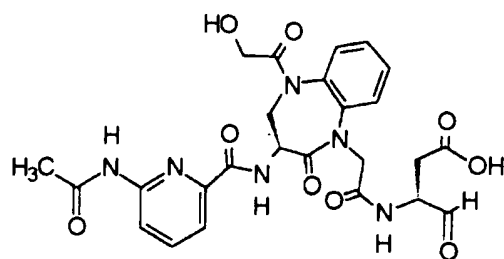
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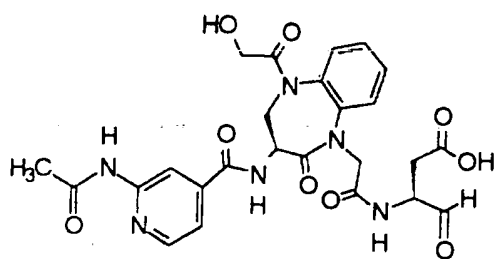


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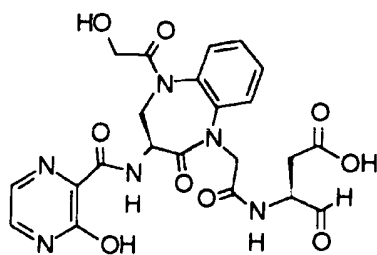
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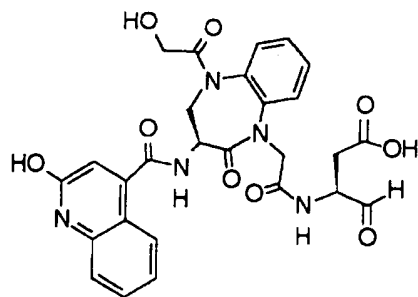
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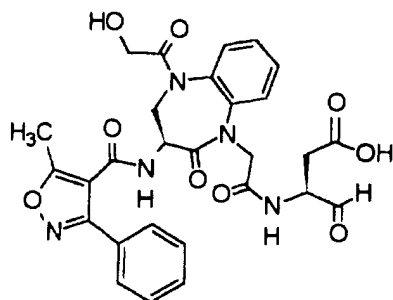


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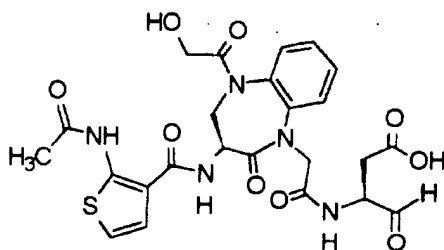


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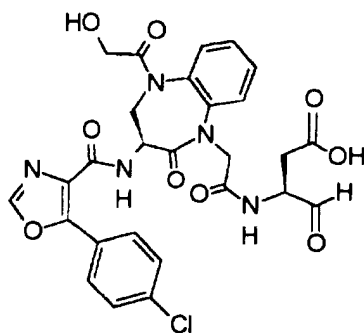


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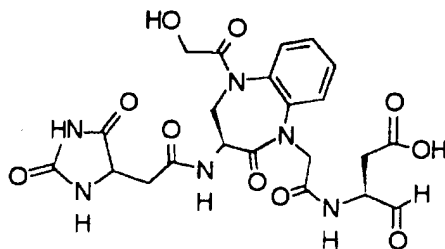


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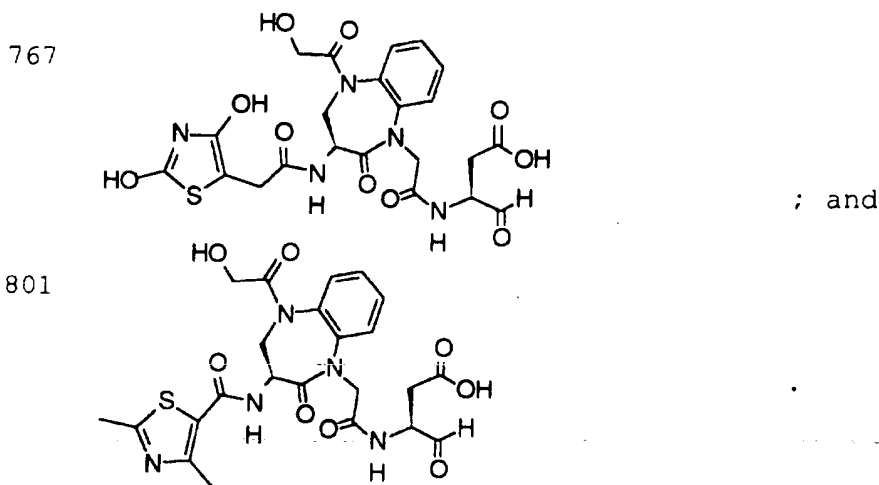
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5 The most preferred compounds of embodiments (K) and (L) are those wherein the Ar<sub>3</sub> cyclic group is isoquinolyl.

Compounds of this invention are described in co-pending United States Application Serial Nos. 10 08/575,641 and 08/598,332 the disclosures of which are herein incorporated by reference.

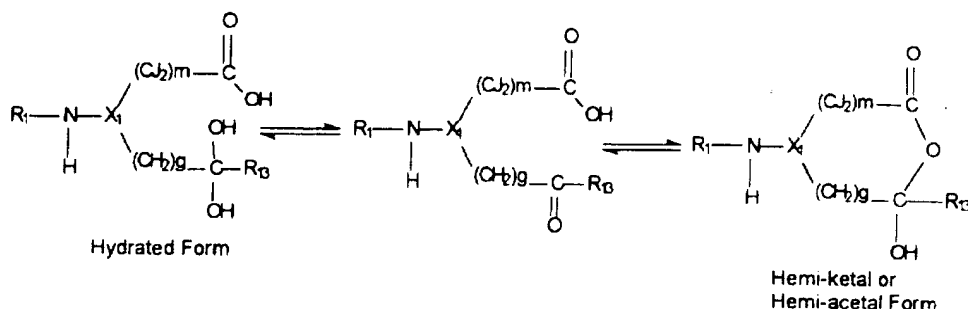
The compounds of this invention have a molecular weight of less than or equal to about 700 Daltons, and more preferably between about 400 and 600 15 Daltons. These preferred compounds may be readily absorbed by the bloodstream of patients upon oral administration. This oral availability makes such compounds excellent agents for orally-administered treatment and prevention regimens against IL-1-, 20 apoptosis-, IGIF- or IFN- $\gamma$  mediated diseases.

It should be understood that the compounds of this invention may exist in various equilibrium forms, depending on conditions including choice of solvent, pH, and others known to the practitioner skilled in the 25 art. All such forms of these compounds are expressly included in the present invention. In particular, many

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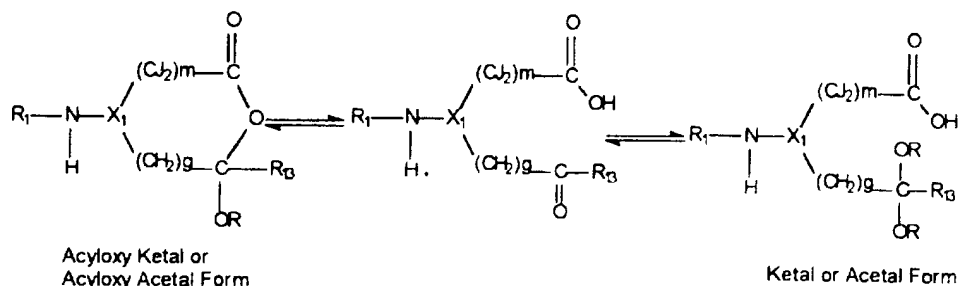
of the compounds of this invention, especially those which contain aldehyde or ketone groups in  $R_3$  and carboxylic acid groups in T, may take hemi-ketal (or hemi-acetal) or hydrated forms. For example, compounds

5 of embodiment (A) may take the forms depicted below:  
EQ1



Depending on the choice of solvent and other conditions known to the practitioner skilled in the art, compounds of this invention may also take acyloxy

10 ketal, acyloxy acetal, ketal or acetal form:



In addition, it should be understood that the equilibrium forms of the compounds of this invention may include tautomeric forms. All such forms of these compounds are expressly included in the present

15 invention.

It should be understood that the compounds of this invention may be modified by appropriate

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functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion. In addition, the compounds may be altered to pro-drug form such that the desired compound is created in the body of the patient as the result of the action of metabolic or other biochemical processes on the pro-drug. Such pro-drug forms typically demonstrate little or no activity in *in vitro* assays. Some examples of pro-drug forms include ketal, acetal, oxime, imine, and hydrazone forms of compounds which contain ketone or aldehyde groups, especially where they occur in the R<sub>3</sub> group of the compounds of this invention. Other examples of pro-drug forms include the hemi-ketal, hemi-acetal, acyloxy ketal, acyloxy acetal, ketal, and acetal forms that are described in EQ1 and EQ2.

#### ICE and TX Cleave and Thereby Activate Pro-IGIF

The ICE protease was identified previously by virtue of its ability to process inactive pro-IL-1 $\beta$  to mature active IL-1 $\beta$ , a pro-inflammatory molecule, in vitro and in vivo. Here we show that ICE and its close homologue TX (Caspase-4, C. Faucheu et al., EMBO, 14, p. 1914 (1995)) can proteolytically cleave inactive pro-IGIF. This processing step is required to convert pro-IGIF to its active mature form, IGIF. Cleavage of pro-IGIF by ICE, and presumably by TX, also facilitates the export of IGIF out of cells.

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We first used transient co-expression of plasmids transfected into Cos cells to determine whether any known members of the ICE/CED-3 protease family can process pro-IGIF to IGIF in cultured cells (Example 23) (Fig. 1A).

Fig. 1A demonstrates that ICE cleaves pro-IGIF in Cos cells co-transfected with plasmids that express pro-IGIF in the presence of active ICE. Cos cells were transfected with an expression plasmid for pro-IGIF alone (lane 2) or in combination with the indicated expression plasmids encoding wild type or inactive mutants of ICE/CED-3 family of proteases (lanes 3-12). Cell lysates were prepared and analyzed for the presence of IGIF protein by immunoblotting with an anti-IGIF antiserum. Lane 1 contained lysates from mock transfected cells.

Co-expression of pro-IGIF with ICE or TX resulted in the cleavage of pro-IGIF into a polypeptide similar in size to the naturally-occurring 18-kDa mature IGIF. This processing event is blocked by single point mutations that alter the catalytic cysteine residues and thus inactivate ICE and TX (Y. Gu et al., EMBO, 14, p. 1923 (1995)).

Co-expression with CPP32 (Caspase-3), a protease involved in programmed cell death (T. Fernandes-Alnemri et al., J. Biol. Chem., 269, p. 30761 (1994); D. W. Nicholson et al., Nature, 376, p. 37 (1995)), resulted in the cleavage of pro-IGIF into a smaller polypeptide, while co-expression with CMH-1 (Caspase-7), a close homolog of CPP32 (J. A. Lippke et al., J. Biol. Chem., 271, p. 1825 (1996)), failed to cleave pro-IGIF to any significant extent. Thus, ICE and TX appear to be capable of cleaving pro-IGIF into a

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polypeptide similar in size to the naturally-occurring 18-kDa IGIF.

We next examined the ability of these cysteine proteases to cleave pro-IGIF in vitro using a purified, recombinant (His)<sub>6</sub>-tagged pro-IGIF as a substrate (**Example 23**).

**Fig. 1B** demonstrates that pro-IGIF is cleaved in vitro by ICE. Purified recombinant (His)<sub>6</sub>-tagged pro-IGIF (2 µg) was incubated with the indicated cysteine protease in the presence or absence of ICE or CPP32 inhibitors as described in **Example 23**. The cleavage products were analyzed by SDS-PAGE and Coomassie Blue staining.

ICE cleaved the 24 kDa pro-IGIF into two polypeptides of approximately 18-kDa and 6-kDa. N-terminal amino acid sequencing of the ICE cleavage products indicated that the 18-kDa polypeptide contains the same N-terminal amino acid residues (Asn-Phe-Gly-Arg-Leu) as the naturally occurring IGIF. This shows that ICE cleaves pro-IGIF at the authentic processing site (Asp35-Asn36) (H. Okamura et al., Infection and Immunity, 63, p. 3966 (1995); H. Okamura et al., Nature, 378, p. 88 (1995)). N-terminal amino acid sequencing of the CPP32 cleavage products indicated that CPP32 cleaved pro-IGIF at Asp69-Ile70.

The cleavage by ICE of pro-IGIF is highly specific with a catalytic efficiency ( $k_{cat}/K_M$ ) of  $1.4 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$  ( $K_M = 0.6 \pm 0.1 \text{ µM}$ ;  $k_{cat} = 8.6 \pm 0.3 \text{ s}^{-1}$ ) and is inhibited by specific ICE inhibitors (Ac-Tyr-Val-Ala-Asp-aldehyde) and Cbz-Val-Ala-Asp-[(2,6-dichlorobenzoyl)oxy]methylketone, (N.A. Thornberry et al., Nature, 356, p. 768 (1992); R. E. Doile et al., J. Med. Chem., 37, p. 563 (1994)).

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Fig. 1C demonstrates that ICE cleavage in vitro activates pro-IGIF. Uncleaved pro-IGIF, ICE- or CPP32-cleaved products of pro-IGIF, or recombinant mature IGIF (rIGIF) were each added to A.E7 cell  
5 cultures to a final concentration of 12 ng/ml or 120 ng/ml (see, **Example 23**). Eighteen hours later, IFN- $\gamma$  in the cultural medium was quantified by ELISA. While the uncleaved pro-IGIF had no detectable IFN- $\gamma$  inducing activity, ICE-cleaved pro-IGIF was active in inducing  
10 IFN- $\gamma$  production in Th1 cells.

Like ICE, the ICE homolog TX also cleaved pro-IGIF into similarly sized polypeptides. However, its catalytic efficiency was about two orders of magnitude lower than that shown for ICE.

15 Consistent with the observations from the Cos cell experiments above, CPP32 cleaved pro-IGIF at a different site (Asp69-Ile70) and the resulting polypeptides had little IFN- $\gamma$  inducing activity (**Fig. 1C**). CMH-1 and granzyme B each failed to cleave  
20 pro-IGIF to any significant extent.

Together, these results demonstrate that, both in Cos cells and in vitro, ICE and TX are capable of processing the inactive pro-IGIF precursor at the authentic maturation site to generate a biologically  
25 active IGIF molecule.

#### Processing of Pro-IGIF by ICE Facilitates Its Export

IGIF is produced by activated Kupffer cells and macrophages in vivo and is exported out of the cells upon stimulation by endotoxin (H. Okamura et al.,  
30 Infection and Immunity, 63, p. 3966 (1995); H. Okamura et al., Nature, 378, p. 88 (1995)). We used the Cos cell co-expression system (**Example 23**) to examine



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whether the intracellular cleavage of pro-IGIF by ICE would facilitate the export of mature IGIF from the cell. Such is the case for pro-IL-1 $\beta$  when it is cleaved by ICE into active IL-1 $\beta$  (N.A. Thornberry et al., Nature, 356, p. 768 (1992)).

In **Fig. 2A**, Cos cells transfected with an expression plasmid for pro-IGIF alone (lanes 2 and 6) or in combination with an expression plasmid encoding wild type (lanes 3 and 7) or inactive mutant ICE (lanes 4 and 8) were metabolically labeled with <sup>35</sup>S-methionine (see, **Example 24**). Cell lysates (left) and conditioned medium (right) were immunoprecipitated with an anti-IGIF antiserum. The immunoprecipitated proteins were analyzed by SDS-PAGE and fluorography (**Fig. 2A**).

An 18-kDa polypeptide corresponding in size to mature IGIF was detected in the conditioned medium of Cos cells co-expressing pro-IGIF and ICE, while Cos cells co-expressing pro-IGIF and an inactive ICE mutant (ICE-C285S), or pro-IGIF alone (-) exported only very low levels of pro-IGIF and no detectable mature IGIF. We estimate that about 10% of the mature IGIF was exported from co-transfected cells, while greater than 99% of pro-IGIF was retained within the cells.

We also measured the presence of IFN- $\gamma$  inducing activity in cell lysates and in the conditioned medium of the above transfected cells (see, **Example 24**). IFN- $\gamma$  inducing activity was detected in both cell lysates and the conditioned medium of Cos cells co-expressing pro-IGIF and ICE, but not in cells expressing either pro-IGIF or ICE alone (**Fig. 2B**).

These results indicate that ICE cleavage of pro-IGIF facilitates the export of mature, active IGIF from cells.

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Pro-IGIF is a Physiological Substrate of ICE In Vivo

To study the role of ICE in the proteolytic activation and export of IGIF under physiological conditions, we examined the processing of pro-IGIF and export of mature IGIF from lipopolysaccharide (LPS)-activated Kupffer cells harvested from Propionibacterium acnes-elicited wild type and ICE deficient (ICE-/-) mice (**Example 25**).

As shown in **Fig. 3A**, Kupffer cells from ICE-/- mice are defective in the export of IGIF. Kupffer cell lysates of wild type and ICE-/- mice contained similar amounts of IGIF as determined by ELISA. IGIF, however, could be detected only in the conditioned medium of wild type but not of the ICE-/- cells. Thus, ICE-deficient (ICE-/-) mice synthesize pro-IGIF, but fail to export it as extracellular pro-or mature IGIF.

To determine whether ICE-deficient (ICE-/-) mice process intracellular pro-IGIF but fail to export IGIF, Kupffer cells from wild type and ICE-/- mice were metabolically labeled with <sup>35</sup>S-methionine and IGIF immunoprecipitation experiments were performed on cell lysates and conditioned media as described in **Example 25**. These experiments demonstrated that unprocessed pro-IGIF was present in both wild type and ICE-/- Kupffer cells. However, the 18-kDa mature IGIF was present only in the conditioned medium of wild type and not ICE-/- Kupffer cells (**Fig. 3B**). This shows that active ICE is required in cells for the export of processed IGIF out of the cell.

In addition, conditioned medium from wild type but not from ICE-/- Kupffer cells contained IFN- $\gamma$  inducing activity that was not attributed to the action

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of IL-12 because it was insensitive to a neutralizing anti-IL-12 antibody. The absence of IGIF in the conditioned medium of ICE-/- Kupffer cells is consistent with the finding in Cos cells that the processing of pro-IGIF by ICE is required for the export of active IGIF.

**Figs. 3C and 3D** show that, in vivo, ICE-/- mice have reduced serum levels of IGIF and IFN- $\gamma$ , respectively. Wild type (ICE+/+) and ICE-/- mice (n=3) primed with heat-inactivated *P. acnes* were challenged with LPS (**Example 26**), and the levels of IGIF (**Fig. 3C**) and IFN- $\gamma$  (**Fig. 3D**) in the sera of challenged mice were measured by ELISA three hours after LPS challenge (**Example 25**).

The sera of ICE-/- mice stimulated by *P. acnes* and LPS contained reduced levels of IGIF (**Fig. 3C**) and no detectable IFN- $\gamma$  inducing activity in the presence of an anti-IL-12 antibody. The reduced serum levels of IGIF likely accounts for the significantly lower levels of IFN- $\gamma$  in the sera of ICE-/- mice (**Fig. 3D**), because we have observed no significant difference in the production of IL-12 in ICE-/- mice under these conditions. Consistent with this interpretation is the finding that non-adherent splenocytes from wild type and ICE-/- mice produced similar amounts of IFN- $\gamma$  when stimulated with recombinant active IGIF in vitro. Thus the impaired production of IFN- $\gamma$  is not due to any apparent defect in the T cells of the ICE-/- mice.

Taken together, these results establish a critical role for ICE in processing the IGIF precursor and in the export of active IGIF both in vitro and in

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vivo.

To examine in more detail the relationship between serum levels of IFN- $\gamma$  and ICE activity in vivo, a time course after challenge of wild type and  
5 ICE-deficient mice with LPS was performed (Example 26) (Fig. 4).

Fig. 4 shows a time course increase of serum IFN- $\gamma$  in wild type mice, with sustained levels of  $\geq 17$  ng/ml occurring from 9-18 hrs after LPS challenge.  
10 As predicted by the experiments discussed above, serum IFN- $\gamma$  levels were significantly lower in ICE-/- mice, with a maximum of 2 ng/ml achieved over the same time period, which is approximately 15% of the level observed in wild type mice (Fig. 4).

15 Animals were also observed for clinical signs of sepsis and body temperature was measured at 4-hour intervals in wild type and ICE-/- mice challenged with 30 mg/kg or 100 mg/kg LPS (ICE-/-only). Results in Fig. 4 show that wild type mice experienced a  
20 significant decrease in body temperature (from 36°C to 26°C) within 12 hours of LPS challenge. Signs of clinical sepsis were evident and all animals expired within 24-28 hours.

In contrast, ICE-/- mice challenged with  
25 30 mg/kg LPS experienced only a 3°-4°C decrease in body temperature with minimal signs of distress and with no observed lethality. ICE-/- mice challenged with 100 mg/kg LPS experienced clinical symptoms, a decrease in body temperature, and mortality similar to wild type  
30 mice at the 30 mg/kg LPS dose.

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The ICE Inhibitor Ac-YVAD-CHO is an Equipotent  
Inhibitor of IL-1 $\beta$  and IFN- $\gamma$  Production

Since the processing and secretion of  
5 biologically active IGIF is mediated by ICE, we  
compared the activity of a reversible ICE inhibitor  
(Ac-YVAD-CHO) on IL-1 $\beta$  and IFN- $\gamma$  production in a  
peripheral blood mononuclear cell (PBMC) assay  
(**Examples 27**).

10 Results in **Fig. 5** show a similar potency for  
the ability of the Ac-YVAD-CHO ICE inhibitor to  
decrease IL-1 $\beta$  and IFN- $\gamma$  production in human PBMCs,  
with an IC<sub>50</sub> of 2.5  $\mu$ M for each. Similar results were  
obtained in studies with wild type mouse splenocytes.

15 These findings provide additional evidence  
that pro-IGIF is a physiological substrate for ICE and  
suggest that ICE inhibitors will be useful tools for  
controlling physiological levels of IGIF and IFN- $\gamma$ .

In summary, we have found that ICE controls  
20 IGIF and IFN- $\gamma$  levels in vivo and in vitro and that ICE  
inhibitors can decrease levels of IGIF and IFN- $\gamma$  in  
human cells. These results have been described in co-  
pending United States Application Serial No.  
08/712,878, the disclosure of which is herein  
25 incorporated by reference.

Compositions and Methods

The pharmaceutical compositions and methods  
of this invention will be useful for controlling IL-1,  
IGIF and IFN- $\gamma$  levels in vivo. The methods and  
30 compositions of this invention will thus be useful for  
treating or reducing the advancement, severity of  
effects of IL-1, IGIF- and IFN- $\gamma$ -mediated conditions.

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The compounds of this invention are effective ligands for ICE. Accordingly, these compounds are capable of targeting and inhibiting events in IL-1-, apoptosis-, IGIF-, and IFN- $\gamma$ -mediated diseases, and, thus, the ultimate activity of that protein in inflammatory diseases, autoimmune diseases, destructive bone, proliferative disorders, infectious diseases, and degenerative diseases. For example, the compounds of this invention inhibit the conversion of precursor IL-1 $\beta$  to mature IL-1 $\beta$  by inhibiting ICE. Because ICE is essential for the production of mature IL-1, inhibition of that enzyme effectively blocks initiation of IL-1-mediated physiological effects and symptoms, such as inflammation, by inhibiting the production of mature IL-1. Thus, by inhibiting IL-1 $\beta$  precursor activity, the compounds of this invention effectively function as IL-1 inhibitors.

Similarly, compounds of this invention inhibit the conversion of precursor IGIF to mature IGIF. Thus, by inhibiting IGIF production, the compounds of this invention effectively function as inhibitors of IFN- $\gamma$  production.

Accordingly, one embodiment of this invention provides a method for decreasing IGIF production in a subject comprising the step of administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of an ICE inhibitor and a pharmaceutically acceptable carrier.

Another embodiment of this invention provides a method for decreasing IFN- $\gamma$  production in a subject comprising the step of administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of an ICE inhibitor and a

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pharmaceutically acceptable carrier.

In another embodiment, the methods of this invention comprise the step of administering to a subject a pharmaceutical composition comprising an inhibitor of an ICE-related protease that is capable of cleaving pro-IGIF to active IGIF, and a pharmaceutically acceptable carrier. One such ICE-related protease is TX, as described above. This invention thus provides methods and pharmaceutical compositions for controlling IGIF and IFN- $\gamma$  levels by administering a TX inhibitor.

Other ICE-related proteases capable of processing pro-IGIF into an active IGIF form may also be found. Thus it is envisioned that inhibitors of those enzymes may be identified by those of skill in the art and will also fall within the scope of this invention.

The compounds of this invention may be employed in a conventional manner for the treatment of diseases which are mediated by IL-1, apoptosis, IGIF or IFN- $\gamma$ . Such methods of treatment, their dosage levels and requirements may be selected by those of ordinary skill in the art from available methods and techniques. For example, a compound of this invention may be combined with a pharmaceutically acceptable adjuvant for administration to a patient suffering from an IL-1-, apoptosis-, IGIF- or IFN- $\gamma$ -mediated disease in a pharmaceutically acceptable manner and in an amount effective to lessen the severity of that disease.

Alternatively, the compounds of this invention may be used in compositions and methods for treating or protecting individuals against IL-1-, apoptosis-, IGIF- or IFN- $\gamma$ -mediated diseases over

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extended periods of time. The compounds may be employed in such compositions either alone or together with other compounds of this invention in a manner consistent with the conventional utilization of ICE inhibitors in pharmaceutical compositions. For example, a compound of this invention may be combined with pharmaceutically acceptable adjuvants conventionally employed in vaccines and administered in, prophylactically effective amounts to protect individuals over an extended period of time against IL-1-, apoptosis-, IGIF- or IFN- $\gamma$ - mediated diseases.

The compounds of this invention may also be co-administered with other ICE inhibitors to increase the effect of therapy or prophylaxis against various IL-1-, apoptosis, IGIF- or IFN- $\gamma$ -mediated diseases.

In addition, the compounds of this invention may be used in combination either conventional anti-inflammatory agents or with matrix metalloprotease inhibitors, lipoxxygenase inhibitors and antagonists of cytokines other than IL-1 $\beta$ .

The compounds of this invention can also be administered in combination with immunomodulators (e.g., bropirimine, anti-human alpha interferon antibody, IL-2, GM-CSF, methionine enkephalin, interferon alpha, diethyldithiocarbamate, tumor necrosis factor, naltrexone and rEPO) or with prostaglandins, to prevent or combat IL-1-mediated disease symptoms such as inflammation.

When the compounds of this invention are administered in combination therapies with other agents, they may be administered sequentially or concurrently to the patient. Alternatively, pharmaceutical or prophylactic compositions according



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to this invention comprise a combination of an ICE inhibitor of this invention and another therapeutic or prophylactic agent.

Pharmaceutical compositions of this invention  
5 comprise any of the compounds of the present invention, and pharmaceutically acceptable salts thereof, with any pharmaceutically acceptable carrier, adjuvant or vehicle. Pharmaceutically acceptable carriers,  
10 adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as  $\alpha$ -tocopherol polyethyleneglycol 1000 succinate, or other similar  
15 polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium  
20 hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers,  
25 polyethylene glycol and wool fat. Cyclodextrins such as  $\alpha$ -,  $\beta$ - and  $\gamma$ -cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2-and 3-hydroxypropyl- $\beta$ -cyclodextrines, or  
30 other solubilized derivatives may also be advantageously used to enhance delivery of compounds of this invention.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by

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inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. We prefer oral administration. The pharmaceutical compositions of this invention may contain any  
5 conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compounds or  
10 its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

15 The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable  
20 dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a  
25 solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending  
30 medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable

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oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant such as Ph. Helv or a similar alcohol.

5 The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, and aqueous suspensions and  
10 solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents  
15 include lactose and dried corn starch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

20 The pharmaceutical compositions of this invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient  
25 which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

30 Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the pharmaceutical

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composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-administered transdermal patches are also included in this invention.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

Dosage levels of between about 0.01 and about 100 mg/kg body weight per day, preferably between about 1 and 50 mg/kg body weight per day of the active ingredient compound are useful in the prevention and treatment of IL-1-, apoptosis, IGF and IFN- $\gamma$ -mediated

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diseases, including inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases, degenerative diseases, necrotic diseases, osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, adult respiratory distress syndrome, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, inflammatory bowel disease, Crohn's disease, psoriasis, graft vs. host disease, osteoporosis, multiple myeloma-related bone disorder, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma sepsis, septic shock, Shigellosis, Alzheimer's disease, Parkinson's disease, cerebral ischemia, myocardial ischemia, spinal muscular atrophy, multiple sclerosis, AIDS-related encephalitis, HIV-related encephalitis, aging, alopecia, and neurological damage due to stroke. Typically, the pharmaceutical compositions of this invention will be administered from about 1 to 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Preferably, such preparations contain from about 20% to about 80% active compound.

Upon improvement of a patient's condition, a

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5 maintenance dose of a compound, composition or  
combination of this invention may be administered, if  
necessary. Subsequently, the dosage or frequency of  
administration, or both, may be reduced, as a function  
10 of the symptoms, to a level at which the improved  
condition is retained when the symptoms have been  
alleviated to the desired level, treatment should  
cease. Patients may, however, require intermittent  
treatment on a long-term basis upon any recurrence or  
disease symptoms.

15 As the skilled artisan will appreciate, lower  
or higher doses than those recited above may be  
required. Specific dosage and treatment regimens for  
any particular patient will depend upon a variety of  
factors, including the activity of the specific  
20 compound employed, the age, body weight, general health  
status, sex, diet, time of administration, rate of  
excretion, drug combination, the severity and course of  
the disease, and the patient's disposition to the  
disease and the judgment of the treating physician.

The IL-1 mediated diseases which may be  
treated or prevented by the compounds of this invention  
include, but are not limited to, inflammatory diseases,  
autoimmune diseases, destructive bone disorders,  
25 proliferative disorders, infectious diseases, and  
degenerative diseases. The apoptosis-mediated diseases  
which may be treated or prevented by the compounds of  
this invention include degenerative diseases.

Inflammatory diseases which may be treated or  
30 prevented include, but are not limited to  
osteoarthritis, acute pancreatitis, chronic  
pancreatitis, asthma, and adult respiratory distress  
syndrome. Preferably the inflammatory disease is  
osteoarthritis or acute pancreatitis.

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Autoimmune diseases which may be treated or prevented include, but are not limited to, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, multiple sclerosis, inflammatory bowel disease, Crohn's disease, psoriasis, and graft vs. host disease. Preferably the autoimmune disease is rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, or psoriasis.

Destructive bone disorders which may be treated or prevented include, but are not limited to, osteoporosis and multiple myeloma-related bone disorder.

Proliferative diseases which may be treated or prevented include, but are not limited to, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, and multiple myeloma.

Infectious diseases which may be treated or prevented include, but are not limited to, sepsis, septic shock, and Shigellosis.

The IL-1-mediated degenerative or necrotic diseases which may be treated or prevented by the compounds of this invention include, but are not limited to, Alzheimer's disease, Parkinson's disease, cerebral ischemia, and myocardial ischemia. Preferably, the degenerative disease is Alzheimer's disease.

The apoptosis-mediated degenerative diseases which may be treated or prevented by the compounds of

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this invention include, but are not limited to, Alzheimer's disease, Parkinson's disease, cerebral ischemia, myocardial ischemia, spinal muscular atrophy, multiple sclerosis, AIDS-related encephalitis, HIV-related encephalitis, aging, alopecia, and neurological damage due to stroke.

The methods of this invention may be used for treating, or reducing the advancement, severity or effects of an IGIF-or IFN- $\gamma$ -mediated inflammatory, autoimmune, infectious, proliferative, destructive bone, necrotic, and degenerative conditions, including diseases, disorders or effects, wherein the conditions are characterized by increased levels of IGIF or IFN- $\gamma$  production.

Examples of such inflammatory conditions include, but are not limited to, osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, cerebral ischemia, myocardial ischemia and adult respiratory distress syndrome.

Preferably, the inflammatory condition is rheumatoid arthritis, ulcerative colitis, Crohn's disease, hepatitis and adult respiratory distress syndrome.

Examples of such infectious conditions include, but are not limited to, infectious hepatitis, sepsis, septic shock and Shigellosis.

Examples of such autoimmune conditions include, but are not limited to, glomerulonephritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), juvenile diabetes, autoimmune hemolytic anemia, autoimmune



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neutropenia, thrombocytopenia, myasthenia gravis, multiple sclerosis, psoriasis, lichenplanus, graft vs. host disease, acute dermatomyositis, eczema, primary cirrhosis, hepatitis, uveitis, Behcet's disease, acute  
5 dermatomyositis, atopic skin disease, pure red cell aplasia, aplastic anemia, amyotrophic lateral sclerosis and nephrotic syndrome.

Preferably the autoimmune condition is glomerulonephritis, insulin-dependent diabetes mellitus  
10 (Type I), juvenile diabetes, psoriasis, graft vs. host disease, including transplant rejection, and hepatitis.

Examples of such destructive bone disorders include, but are not limited to, osteoporosis and multiple myeloma-related bone disorder.

15 Examples of such proliferative conditions include, but are not limited to, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, and multiple myeloma.

Examples of such neurodegenerative conditions  
20 include, but are not limited to, Alzheimer's disease, Parkinson's disease and Huntington's disease.

Although this invention focuses on the use of the compounds disclosed herein for preventing and treating IL-1, apoptosis, IGIF- and IFN- $\gamma$ -mediated  
25 diseases, the compounds of this invention can also be used as inhibitory agents for other cysteine proteases.

The compounds of this invention are also useful as commercial reagents which effectively bind to ICE or other cysteine proteases. As commercial  
30 reagents, the compounds of this invention, and their derivatives, may be used to block proteolysis of a target peptide in biochemical or cellular assays for ICE and ICE homologs or may be derivatized to bind to a

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stable resin as a tethered substrate for affinity chromatography applications. These and other uses which characterize commercial cystine protease inhibitors will be evident to those of ordinary skill in the art.

#### Process of Preparing N-Acylamino Compounds

The ICE inhibitors of this invention may be synthesized using conventional techniques.

Advantageously, these compounds are conveniently synthesized from readily available starting materials.

The compounds of this invention are among the most readily synthesized ICE inhibitors known. Previously described ICE inhibitors often contain four or more chiral centers and numerous peptide linkages. The relative ease with which the compounds of this invention can be synthesized represents an advantage in the large scale production of these compounds.

For example, compounds of this invention may be prepared using the processes described herein. As can be appreciated by the skilled practitioner, these processes are not the only means by which the compounds described and claimed in this application may be synthesized. Further methods will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps described herein may be performed in an alternate sequence or order to give the desired compounds.

This invention also provides a preferred method for preparing the compounds of this invention. Accordingly, in another embodiment (M) is provided a process for preparing an N-acylamino compound comprising the steps of:

a) mixing a carboxylic acid with an N-

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alloc-protected amino in the presence of an inert solvent, triphenylphosphine, a nucleophilic scavenger, and tetrakis-triphenyl phosphine palladium(0) at ambient temperature under an inert atmosphere; and

5           b) adding to the step a) mixture, HOBT and EDC; and optionally comprising the further step of:

          c) hydrolyzing the step b) mixture in the presence of a solution comprising an acid and H<sub>2</sub>O, wherein the step b) mixture is optionally concentrated, prior to hydrolyzing.

10           Preferably, the inert solvent is CH<sub>2</sub>Cl<sub>2</sub>, DMF, or a mixture of CH<sub>2</sub>Cl<sub>2</sub> and DMF.

          Preferably, the nucleophilic scavenger is dimedone, morpholine, trimethylsilyl dimethylamine, or dimethyl barbituric acid. More preferably, the nucleophilic scavenger is trimethylsilyl dimethylamine or dimethyl barbituric acid.

15           Preferably, the solution comprises trifluoroacetic acid in about 1-90% by weight. More preferably, the solution comprises trifluoroacetic acid in about 20-50% by weight.

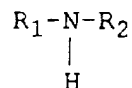
          Alternatively, the solution comprises hydrochloric acid in about 0.1-30% by weight. More preferably, the solution comprises hydrochloric acid in about 0.1-30% by weight.

25           More preferably, in the above process, the inert solvent is CH<sub>2</sub>Cl<sub>2</sub>, DMF, or a mixture of CH<sub>2</sub>Cl<sub>2</sub> and DMF and the nucleophilic scavenger is dimedone, morpholine, trimethylsilyl dimethylamine, or dimethyl barbituric acid.

30           Most preferably, in the above process the inert solvent is CH<sub>2</sub>Cl<sub>2</sub>, DMF, or a mixture of CH<sub>2</sub>Cl<sub>2</sub> and DMF and the nucleophilic scavenger is trimethylsilyl dimethylamine or dimethyl barbituric acid.

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Preferably, the N-acyclamino compound is represented by formula (VIII):



5

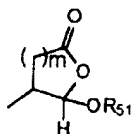
wherein:

R<sub>1</sub> is as defined above in embodiment (A);

R<sub>2</sub> is:

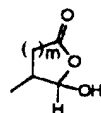
10

(a)



wherein R<sub>51</sub> is as defined above in embodiment (B);

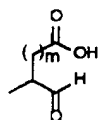
(b)



, or

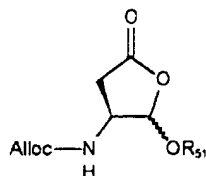
15

(c)



;

Preferably, the N-alloc-protected amine is:



, wherein R<sub>51</sub> is as defined above.

20 In preferred processes, the substituents are as defined in embodiment (A).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein R<sub>1</sub> is as defined

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above in embodiment (B) and  $R_2$  is as defined above in embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in  
5 embodiment (B).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein  $R_1$  is as defined above in embodiment (C) and  $R_2$  is as defined above in  
10 embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in  
10 embodiment (C).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein  $R_1$  is as defined  
15 above in embodiment (D) and  $R_2$  is as defined above in embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in  
embodiment (D).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein  $R_1$  is as defined  
20 above in embodiment (E) and  $R_2$  is as defined above in embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in  
25 embodiment (E).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein  $R_1$  is as defined  
above in embodiment (F) and  $R_2$  is as defined above in  
30 embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in  
embodiment (F).

Alternatively, the N-acylamino compound is

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represented by formula (VIII), wherein  $R_1$  is as defined above in embodiment (G) and  $R_2$  is as defined above in embodiment (G).

Preferably in these alternative  
5 processes, the substituents are as defined above in embodiment (G).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein  $R_1$  is as defined above in embodiment (H) and  $R_2$  is as defined above in  
10 embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in embodiment (H).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein  $R_1$  is as defined above in embodiment (I) and  $R_2$  is as defined above in  
15 embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in  
20 embodiment (I).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein  $R_1$  is as defined above in embodiment (J) and  $R_2$  is as defined above in embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in  
25 embodiment (J).

Alternatively, the N-acylamino compound is represented by formula (VIII), wherein  $R_1$  is as defined above in embodiment (K) and  $R_2$  is as defined above in  
30 embodiment (M).

Preferably in these alternative processes, the substituents are as defined above in embodiment (K).

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Alternatively, the N-acylamino compound is represented by formula (VIII), wherein  $R_1$  is as defined above in embodiment (L) and  $R_2$  is as defined above in embodiment (M).

5                    Preferably in these alternative processes, the substituents are as defined above in embodiment (L).

In order that this invention be more fully understood, the following examples are set forth.

10                   These examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.

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Example 1

Inhibition of ICE

We obtained inhibition constants ( $K_i$ ) and  $IC_{50}$  values for compounds of this invention using the three methods described below:

1. Enzyme assay with UV-visible substrate

This assay is run using an Succinyl-Tyr-Val-Ala-Asp-pNitroanilide substrate. Synthesis of analogous substrates is described by L. A. Reiter (Int. J. Peptide Protein Res. 43, 87-96 (1994)). The assay mixture contains:

65  $\mu$ l buffer (10mM Tris, 1 mM DTT, 0.1% CHAPS @pH 8.1)  
10  $\mu$ l ICE (50 nM final concentration to give a rate of ~1mOD/min)  
5  $\mu$ l DMSO/Inhibitor mixture  
20 20  $\mu$ l 400 $\mu$ M Substrate (80  $\mu$ M final concentration)  
100 $\mu$ l total reaction volume

The visible ICE assay is run in a 96-well microtiter plate. Buffer, ICE and DMSO (if inhibitor is present) are added to the wells in the order listed. The components are left to incubate at room temperature for 15 minutes starting at the time that all components are present in all wells. The microtiter plate reader is set to incubate at 37 °C. After the 15 minute incubation, substrate is added directly to the wells and the reaction is monitored by following the release of the chromophore (pNA) at 405 - 603 nm at 37 °C for 20 minutes. A linear fit of the data is performed and the rate is calculated in mOD/min. DMSO is only present during experiments involving inhibitors, buffer is used to make up the volume to 100  $\mu$ l in the other experiments.



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## 2. Enzyme Assay with Fluorescent Substrate

This assay is run essentially according to Thornberry et al. (Nature 356: 768-774 (1992)), using substrate 17 referenced in that article. The substrate is: Acetyl-Tyr-Val-Ala-Asp-amino-4-methylcoumarin (AMC). The following components are mixed:

65  $\mu$ l buffer (10mM Tris, 1mM DTT, 0.1% CHAPS @pH8.1)  
10  $\mu$ l ICE (2 - 10 nM final concentration)  
5  $\mu$ l DMSO/inhibitor solution  
10 20  $\mu$ l 150  $\mu$ M Substrate (30  $\mu$ M final)  
100  $\mu$ l total-reaction volume

The assay is run in a 96 well microtiter plate. Buffer and ICE are added to the wells. The components are left to incubate at 37 °C for 15 minutes in a temperature-controlled wellplate. After the 15 minute incubation, the reaction is started by adding substrate directly to the wells and the reaction is monitored @37 °C for 30 minutes by following the release of the AMC fluorophore using an excitation wavelength for 380 nm and an emission wavelength of 460 nm. A linear fit of the data for each well is performed and a rate is determined in fluorescence units per second.

For determination of enzyme inhibition constants ( $K_i$ ) or the mode of inhibition (competitive, uncompetitive or noncompetitive), the rate data determined in the enzyme assays at varying inhibitor concentrations are computer-fit to standard enzyme kinetic equations (see I. H. Segel, Enzyme Kinetics, Wiley-Interscience, 1975).

The determination of second order rate constants for irreversible inhibitors was performed by fitting the fluorescence vs time data to the progress equations of Morrison. Morrison, J.F., Mol. Cell.

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Biophys., 2, pp. 347-368 (1985). Thornberry et al. have published a description of these methods for measurement of rate constants of irreversible inhibitors of ICE. Thornberry, N.A., et al.

- 5 Biochemistry, 33, pp. 3923-3940 (1994). For compounds where no prior complex formation can be observed kinetically, the second order rate constants ( $k_{inact}$ ) are derived directly from the slope of the linear plots of  $k_{obs}$  vs.  $[I]$ . For compounds where prior complex
- 10 formation to the enzyme can be detected, the hyperbolic plots of  $k_{obs}$  vs.  $[I]$  are fit to the equation for saturation kinetics to first generate  $K_i$  and  $k'$ . The second order rate constant  $k_{inact}$  is then given by  $k'/K_i$ .

15 3. PBMC Cell assay

IL-1 $\beta$  Assay with a Mixed Population of Human  
Peripheral Blood Mononuclear Cells (PBMC)  
or Enriched Adherent Mononuclear Cells

- Processing of pre-IL-1 $\beta$  by ICE can be
- 20 measured in cell culture using a variety of cell sources. Human PBMC obtained from healthy donors provides a mixed population of lymphocyte subtypes and mononuclear cells that produce a spectrum of
- interleukins and cytokines in response to many classes
- 25 of physiological stimulators. Adherent mononuclear cells from PBMC provides an enriched source of normal monocytes for selective studies of cytokine production by activated cells.

Experimental Procedure:

- 30 An initial dilution series of test compound in DMSO or ethanol is prepared, with a subsequent dilution into RPMI-10% FBS media (containing 2 mM L-glutamine, 10 mM HEPES, 50 U and 50 ug/ml pen/strep)

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respectively to yield drugs at 4x the final test concentration containing 0.4% DMSO or 0.4% ethanol. The final concentration of DMSO is 0.1% for all drug dilutions. A concentration titration which brackets  
5 the apparent  $K_i$  for a test compound determined in an ICE inhibition assay is generally used for the primary compound screen.

Generally 5-6 compound dilutions are tested and the cellular component of the assay is performed in  
10 duplicate, with duplicate ELISA determinations on each cell culture supernatant.

#### PBMC Isolation and IL-1 Assay:

Buffy coat cells isolated from one pint human blood (yielding 40-45 ml final volume plasma plus  
15 cells) are diluted with media to 80 ml and LeukoPREP separation tubes (Becton Dickinson) are each overlaid with 10 ml of cell suspension. After 15 min centrifugation at 1500-1800 xg, the plasma/media layer is aspirated and then the mononuclear cell layer is  
20 collected with a Pasteur pipette and transferred to a 15 ml conical centrifuge tube (Corning). Media is added to bring the volume to 15 ml, gently mix the cells by inversion and centrifuge at 300 xg for 15 min. Resuspend the PBMC pellet in a small volume of media,  
25 count cells and adjust to  $6 \times 10^6$  cells/ml.

For the cellular assay, 1.0 ml of the cell suspension is added to each well of a 24-well flat bottom tissue culture plate (Corning), 0.5 ml test compound dilution and 0.5 ml LPS solution (Sigma  
30 #L-3012; 20 ng/ml solution prepared in complete RPMI media; final LPS concentration 5 ng/ml). The 0.5 ml additions of test compound and LPS are usually sufficient to mix the contents of the wells. Three control mixtures are run per experiment, with either

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LPS alone, solvent vehicle control, and/or additional media to adjust the final culture volume to 2.0 ml. The cell cultures are incubated for 16-18 hr at 37 °C in the presence of 5% CO<sub>2</sub>.

5           At the end of the incubation period, cells are harvested and transferred to 15 ml conical centrifuge tubes. After centrifugation for 10 min at 200 xg, supernatants are harvested and transferred to 1.5 ml Eppendorf tubes. It may be noted that the cell  
10 pellet may be utilized for a biochemical evaluation of pre-IL-1 $\beta$  and/or mature IL-1 $\beta$  content in cytosol extracts by western blotting or ELISA with pre-IL-1 $\beta$  specific antisera.

Isolation of Adherent Mononuclear cells:

15           PBMC are isolated and prepared as described above. Media (1.0 ml) is first added to wells followed by 0.5 ml of the PBMC suspension. After a one hour incubation, plates are gently shaken and nonadherent cells aspirated from each well. Wells are then gently  
20 washed three times with 1.0 ml of media and final resuspended in 1.0 ml media. The enrichment for adherent cells generally yields 2.5-3.0 x 10<sup>5</sup> cells per well. The addition of test compounds, LPS, cell incubation conditions and processing of supernatants  
25 proceeds as described above.

ELISA:

We have used Quantikine kits (R&D Systems) for measurement of mature IL-1 $\beta$ . Assays are performed according to the manufacturer's directions. Mature  
30 IL-1 $\beta$  levels of about 1-3 ng/ml in both PBMC and adherent mononuclear cell positive controls are observed. ELISA assays are performed on 1:5, 1:10 and 1:20 dilutions of supernatants from LPS-positive

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controls to select the optimal dilution for supernatants in the test panel.

The inhibitory potency of the compounds can be represented by an  $IC_{50}$  value, which is the  
5 concentration of inhibitor at which 50% of mature IL-1 $\beta$  is detected in the supernatant as compared to the positive controls.

The skilled practitioner realizes that values obtained in cell assays, such as those described  
10 herein, can depend on multiple factors, such as cell type, cell source, growth conditions and the like.

#### Example 2

##### Pharmacokinetic Studies in the Mouse

15 Peptidyl ICE inhibitors are cleared rapidly with clearance rates greater than 100  $\mu$ /min/kg. Compounds with lower clearance rates have improved pharmacokinetic properties relative to peptidyl ICE inhibitors.

20 We obtained the rate of clearance in the mouse ( $\mu$ /min/kg) for several compounds of this invention using the method described below:

##### Sample Preparation and Dosing

Compounds were dissolved in sterile TRIS  
25 solution (0.02M or 0.05M) at a concentration of 2.5mg/ml. Where necessary to ensure a complete solution, the sample was first dissolved in a minimum of dimethylacetamide (maximum of 5% of total solution volume) then diluted with the TRIS solution.

30 The drug solution was administered to CD-1 mice (Charles River Laboratories - 26-31g) via the tail

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vein at a dose volume of 10ml/kg giving a drug dose of 25mg/kg.

Mice were dosed in groups of 5 for each timepoint (generally from 2 minutes to 2 hours) then at the appropriate time the animals were anaesthetised with halothane and the blood collected into individual heparinized tubes by jugular severance. The blood samples were cooled to 0 °C then the plasma separated and stored at -20 °C until assayed.

#### 10 Bioassay

Drug concentration in the plasma samples were determined by HPLC analysis with UV or MS (ESP) detection. Reverse phase chromatography was employed using a variety of bonded phases from C1 to C18 with eluents composed of aqueous buffer/acetonitrile mixtures run under isocratic conditions.

Quantitation was by external standard methods with calibration curves constructed by spiking plasma with drug solutions to give concentrations in the range of 0.5 to 50µg/ml.

Prior to analysis the plasma samples were deproteinated by the addition of acetonitrile, methanol, trichloroacetic acid or perchloric acid followed by centrifugation at 10,000g for 10 minutes. Sample volumes of 20µl to 50µl were injected for analysis.

#### Compound 214e

##### Dosing and sampling

The drug was dissolved in sterile 0.02M Tris to give a 2.5mg/ml solution which was administered to 11 groups of 5 male CD-1 mice via the tail vein at a dose of 25mg/kg. At each of the following timepoints: 2, 5, 10, 15, 20, 30, 45, 60, 90 and 120 minutes a

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group of animals was anaesthetised and the blood collected into heparinized tubes. After separation the plasma was stored at -20 °C until assayed.

#### Assay

- 5 Aliquots of plasma (150µl) were treated with 5% perchloric acid (5µl) then mixed by vortexing and allowed to stand for 90 minutes prior to centrifugation. The resulting supernatant was separated and 20µl was injected for HPLC analysis.

10 HPLC Conditions

Column	100 x 4.6mm	Kromasil KR 100 5C4
Mobile Phase	0.1M Tris pH7.5	86%
	Acetonitrile	14%
Flowrate	1ml/min	
15 Detection	UV at 210nm	
Retention Time	3.4 mins	

The results of the analysis indicated a decrease in the mean plasma level of the drug from ~ 70µg/ml at 2 minutes to < 2µg/ml at 90 and 120 minutes.

20 Compound 217e

#### Dosing and sampling

- The drug was dissolved in sterile 0.02M Tris to give a 2.5mg/ml solution which was administered to 11 groups of 5 male CD-1 mice via the tail vein at a
- 25 dose of 25mg/kg. At each of the following timepoints: 2, 5, 10, 15, 20, 30, 45, 60, 90 and 120 minutes a group of animals was anaesthetised and the blood collected into heparinized tubes. After separation the plasma was stored at -20 °C until assayed.

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Assay

Aliquots of plasma (100 $\mu$ l) were diluted with acetonitrile (100 $\mu$ l) then mixed by vortexing for 20 seconds before centrifugation for 10 minutes. The resulting supernatant was separated and 20 $\mu$ l was injected for HPLC analysis.

HPLC Conditions

Column	150 x 4.6mm	Zorbax SBC8
Mobile Phase	0.05M Phosphate buffer pH7.1	72%
	Acetonitrile	28%
Flowrate	1.4ml/min	
Detection	UV at 210nm	
Retention Time	3.0 and 3.6 mins (diastereomers)	

The results of the analysis indicated a decrease in mean plasma concentrations from ~ 55 $\mu$ g/ml at 2 minutes to < 0.2 $\mu$ g/ml at 60-120 minutes.

Example 3

Peptidyl ICE inhibitors are cleared rapidly with clearance rates greater than 80 ml/min/kg. Compounds with lower clearance rates have improved pharmacokinetic properties relative to peptidyl ICE inhibitors.

We obtained the rate of clearance in the rat (ml/min/kg) for several compounds of this invention using the method described below:

In vivo Rat Clearance Assay

Cannulations of the jugular and carotid vessels of rats under anesthesia were performed one day prior to the pharmacokinetic study. M.J. Free, R.A.



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Jaffee; 'Cannulation techniques for the collection blood and other bodily fluids'; in: Animal Models; p. 480-495; N.J. Alexander, Ed.; Academic Press; (1978). Drug (10mg/mL) was administered via the

5 jugular vein in a vehicle usually consisting of: propylene glycol/saline, containing 100mM sodium bicarbonate in a 1:1 ratio. Animals were dosed with 10-20 mg drug/kg and blood samples were drawn at 0, 2, 5, 7, 10, 15, 20, 30, 60, and 90 minutes from an

10 indwelling carotid catheter. The blood was centrifuged to plasma and stored at -20 °C until analysis. Pharmacokinetic analysis of data was performed by non-linear regression using standard software such as RStrip (MicroMath Software, UT) and/or Pcnonlin (SCI

15 Software, NC) to obtain clearance values.

Analytical:

Rat plasma was extracted with an equal volume of acetonitrile (containing 0.1% TFA). Samples were then centrifuged at approximately 1,000 x g and the

20 supernatant analyzed by gradient HPLC. A typical assay procedure is described below.

200 µL of plasma was precipitated with 200 µL of 0.1% trifluoroacetic acid (TFA) in acetonitrile and 10 µL of a 50% aqueous zinc chloride solution, vortexed

25 then centrifuged at ~1000 x g and the supernatant collected and analyzed by HPLC.

## HPLC procedure:

Column: Zorbax SB-CN (4.6 x 150 mm) (5µ particle size)

30 Column temperature: 50 °C

Flow rate: 1.0 mL/min

Injection volume: 75 µL.

Mobile phase: A=0.1% TFA in water and B=100% acetonitrile

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Gradient employed: 100% A to 30% A in 15.5 min  
0% A at 16 min  
100% A at 19.2 min  
Wavelength: 214 nm

- 5 A standard curve was run at 20, 10, 5, 2 and  
1 µg/mL concentrations.

#### Example 4

##### Whole Blood Assay for IL-1 $\beta$ Production

- We obtained IC<sub>50</sub> values for several compounds  
10 of this invention using the method described below:

##### Purpose:

- The whole blood assay is a simple method for  
measuring the production of IL-1 $\beta$  (or other cytokines)  
and the activity of potential inhibitors. The  
15 complexity of this assay system, with its full  
complement of lymphoid and inflammatory cell types,  
spectrum of plasma proteins and red blood cells is an  
ideal in vitro representation of human in vivo  
physiologic conditions.

##### 20 Materials:

- Pyrogen-free syringes (~ 30 cc)  
Pyrogen-free sterile vacuum tubes containing  
lyophilized Na<sub>2</sub>EDTA (4.5 mg/10 ml tube)  
Human whole blood sample (~ 30-50 cc)  
25 1.5 ml eppendorf tubes  
Test compound stock solutions (~ 25mM in DMSO or other  
solvent)  
Endotoxin-free sodium chloride solution (0.9%) and HBSS  
Lipopolysaccharide (Sigma; Cat.# L-3012) stock solution  
30 at 1mg/ml in HBSS

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IL-1 $\beta$  ELISA Kit (R & D Systems; Cat # DLB50)

TNF $\alpha$  ELISA Kit (R & D Systems; Cat # DTA50)

Water bath or incubator

Whole Blood Assay Experimental Procedure:

5                   Set incubator or water bath at 30 °C.

Aliquot 0.25ml of blood into 1.5 ml eppendorf tubes.

**Note:** be sure to invert the whole blood sample tubes  
after every two aliquots. Differences in replicates

may result if the cells sediment and are not uniformly  
10   suspended. Use of a positive displacement pipette will  
also minimize differences between replicate aliquots.

Prepare drug dilutions in sterile pyrogen-  
free saline by serial dilution. A dilution series  
which brackets the apparent  $K_i$  for a test compound  
15   determined in an ICE inhibition assay is generally used  
for the primary compound screen. For extremely  
hydrophobic compounds, we have prepared compound  
dilutions in fresh plasma obtained from the same blood  
donor or in PBS-containing 5% DMSO to enhance  
20   solubility.

Add 25  $\mu$ l test compound dilution or vehicle  
control and gently mix the sample. Then add 5.0  $\mu$ l LPS  
solution (250 ng/ml stocked prepared fresh: 5.0 ng/ml  
final concentration LPS), and mix again. Incubate the  
25   tubes at 30 °C in a water bath for 16-18 hr with  
occasional mixing. Alternatively, the tubes can be  
placed in a rotator set at 4 rpm for the same  
incubation period. This assay should be set up in  
duplicate or triplicate with the following controls:  
30   negative control- no LPS; positive control- no test  
inhibitor; vehicle control- the highest concentration  
of DMSO or compound solvent used in the experiment.

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Additional saline is added to all control tubes to normalize volumes for both control and experimental whole blood test samples

After the incubation period, whole blood .  
5 samples are centrifuged for 10 minutes at ~ 2000 rpm in the microfuge, plasma is transferred to a fresh microfuge tube and centrifuged at 1000 x g to pellet residual platelets if necessary. Plasma samples may be stored frozen at -70 °C prior to assay for cytokine  
10 levels by ELISA.

#### ELISA:

We have used R & D Systems (614 McKinley Place N.E. Minneapolis, MN 55413) Quantikine kits for measurement of IL-1 $\beta$  and TNF- $\alpha$ . The assays are  
15 performed according to the manufacturer's directions. We have observed IL-1 $\beta$  levels of ~ 1-5 ng/ml in positive controls among a range of individuals. A 1:200 dilution of plasma for all samples has been sufficient in our experiments for ELISA results to fall  
20 on the linear range of the ELISA standard curves. It may be necessary to optimize standard dilutions if you observe differences in the whole blood assay. Nerad, J.L. et al., J. Leukocyte Biol., 52, pp. 687-692 (1992).

25

#### Example 5

##### Inhibition of ICE homologs

#### 1. Isolation of ICE homologs

Expression of TX in insect cells using a baculovirus expression system. We have subcloned Tx cDNA (Faucheu  
30 et al., supra 1995) into a modified pVL1393 transfer

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vector, co-transfected the resultant plasmid (pVL1393/TX) into insect cells with viral DNA and identified the recombinant baculovirus. After the generation of high titer recombinant virus stock, the medium was examined for TX activity using the visible ICE assay. Typically, infection of *Spodoptera frugiperda* (Sf9) insect cells at an MOI of 5 with recombinant virus stock resulted in a maximum expression after 48 hours of 4.7µg/ml. ICE was used as a standard in the assay.

Amino terminal T7 tagged versions of ICE or TX were also expressed. Designed originally to assist the identification and purification of the recombinant proteins, the various constructs have also allowed examination of different levels of expression and of the relative levels of apoptosis experienced by the different homologs. Apoptosis in the infected Sf9 cells (examined using a Trypan Blue exclusion assay) was increased in the lines expressing ICE or TX relative to cells infected with the viral DNA alone.

**Expression and purification of N-terminally (His)<sub>6</sub>-tagged CPP32 in *E. coli*.** A cDNA encoding a CPP32 (Fernandes-Alnemri et al, supra 1994) polypeptide starting at Ser (29) was PCR amplified with primers that add in frame XhoI sites to both the 5' and 3' ends of the cDNA and the resulting XhoI fragment ligated into a Xho I-cut pET-15b expression vector to create an in frame fusion with (his)<sub>6</sub> tag at the n-terminus of the fusion protein. The predicted recombinant protein starts with the amino acid sequence of MGSSHHHHHHSSGLVPRGSHMLE, where LVPRGS represents a thrombin cleavage site, followed by CPP32 starting at

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Ser (29). *E. coli* BL21(DE3) carrying the plasmid were grown to log phase at 30 °C and were then induced with 0.8 mM IPTG. Cells were harvested two hours after IPTG addition. Lysates were prepared and soluble proteins  
5 were purified by Ni-agarose chromatography. All of the expressed CPP32 protein was in the processed form. N-terminal sequencing analysis indicated that the processing occurred at the authentic site between Asp (175) and Ser (176). Approximately 50 µg of CPP32  
10 protein from 200 ml culture. As determined by active site titration, the purified proteins were fully active. The protease preparation were also very active in vitro in cleaving PARP as well as the synthetic DEVD-AMC substrate (Nicholson et al, supra 1995).

## 15 2. Inhibition of ICE homologs

The selectivity of a panel of reversible inhibitors for ICE homologs is depicted in Table 1. ICE enzyme assays were performed according to Wilson et al (supra 1994) using a YVAD-AMC substrate (Thornberry et al, supra  
20 1992). Assay of TX activity was performed using the ICE substrate under identical conditions to ICE. Assay of CPP32 was performed using a DEVD-AMC substrate (Nicholson et al., supra 1995). In general, there is low selectivity between ICE and TX for a wide range of  
25 scaffolds. None of the synthetic ICE compounds tested are effective inhibitors of CPP32. Assay of the reversible compounds at the highest concentration (1 µM) revealed no inhibition.

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Table 1

Compound	K <sub>i</sub> ICE (nM)	K <sub>i</sub> TX (nM)	K <sub>i</sub> CPP32 (nM)
214e	7.5	7.0 ± 1.1	> 1000
135a	90	55 ± 9	>1000
5 125b	60	57 ± 13	> 1000
137	40	40 ± 7	> 1000

Second-order rate constants for inactivation of ICE and ICE homologs with selected irreversible inhibitors are presented below (Table 2). The irreversible compounds studied are broad spectrum inhibitors of ICE and its homologs. Some selectivity, however, is observed with the irreversible compounds comparing inhibition of ICE and CPP32.

Table 2

Compound	k <sub>inact</sub> (ICE) M <sup>-1</sup> s <sup>-1</sup>	k <sub>inact</sub> (TX) M <sup>-1</sup> s <sup>-1</sup>	k <sub>inact</sub> (CPP32) M <sup>-1</sup> s <sup>-1</sup>
138	120,000	150,000	550,000
217d	475,000	250,000	150,000
108a	100,000	25,000	nd

Example 620 Inhibition of apoptosis

**Fas-Induced Apoptosis in U937 cells.** Compounds were evaluated for their ability to block anti-Fas-induced apoptosis. In a preliminary experiment using RT-PCR, we detected mRNA encoding ICE, TX, ICH-1, CPP32 and

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CMH-1 in unstimulated U937 cells. We used this cell line for apoptosis studies. U937 cells were seeded in culture at  $1 \times 10^5$  cells/ml and grown to  $\sim 5 \times 10^6$  cells/ml. For apoptosis experiments,  $2 \times 10^6$  cells  
5 were plated in 24-well tissue culture plates in 1 ml RPMI-1640-10% FBS and stimulated with 100 ng/ml anti-Fas antigen antibody (Medical and Biological Laboratories, Ltd.). After a 24 hr incubation at 37 °C, the percentage of apoptotic cells was determined by  
10 FACS analysis using ApoTag reagents.

All compounds were tested initially at 20  $\mu$ M and titrations were performed with active compounds to determine IC<sub>50</sub> values. Inhibition of apoptosis (> 75% at 20  $\mu$ M) was observed for 108a, 136, and 138.  
15 An IC<sub>50</sub> of 0.8  $\mu$ M was determined for 217e compared to no inhibition of anti-Fas-induced apoptosis by 214e at 20  $\mu$ M.

#### Example 7

#### In vivo acute assay for efficacy as 20 anti-inflammatory agent

##### **LPS-Induced IL-1 $\beta$ Production.**

Efficacy of 214e and 217e was evaluated in CD1 mice (n=6 per condition) challenged with LPS (20 mg/kg IP). The test compounds were prepared in olive  
25 oil:DMSO:ethanol (90:5:5) and administered by IP injection one hour after LPS. Blood was collected seven hours after LPS challenge. Serum IL-1 $\beta$  levels were measure by ELISA. Results in Fig. 6 show a dose dependent inhibition of IL-1 $\beta$  secretion by 214e, with



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an ED<sub>50</sub> of approximately 15 mg/kg. Similar results were obtained in a second experiment. A significant inhibition of IL-1 $\beta$  secretion was also observed in 217e treated mice (Fig. 7). However, a clear dose response was not apparent.

Compounds 214e and 217e (50 mg/kg) were also administered by oral gavage to assess absorption. Results in Fig. 8 show that 214e, but not 217e when administered orally inhibited IL-1 $\beta$  secretion, suggesting potential for oral efficacy of ICE inhibitors as anti-inflammatory agents.

The efficacy of analogs of 214e were also evaluated in LPS challenged mice after IP administration (Fig. 9) and PO administration (Fig. 10).

**Table 3** % Inhibition of IL- $\beta$  production by analogs of 214e in LPS-challenged mice after PO and IP administration (50 mg/kg).

**Table 3**

Compound	PO% Inhibition	IP% Inhibition
214e	75	78
265	27	30
416	52	39
434	80	74
438	13	40
442	10	0
2002	-	78

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Table 4

Comparison of 214e Prodrugs for  
Efficacy in LPS Challenged Mice:  
Time Course Inhibition of IL-1 $\beta$  Production

Time of Compound Administration (relative to time of LPS challenge, PO, 50 mg/kg)				
Compound	-2 hr	-1 hr	0 hr	+1 hr
214e	39* 43* -*	-* 44* -*	80* 48* -*	55% 75* 11* 47*
304a	30	33	68	37
2100e	49	54	94	66
2100a	8	71	67	58
213e	0	48	41	89
302	0	27	21	26
2100c	0	0	85	40
2100d	42	35	52	26
2100b	0	0	47	26
2001	~63 64*	~62 62*	~57 58*	~54 55*

\* Values obtained in subsequent assays

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Example 8Measurement of blood levels of prodrugs of 214e.

Mice were administered a p.o. dose of compounds **302** and **304a** (50 mg/kg) prepared in 0.5 % carboxymethylcellulose. Blood samples were collected at 1 and 7 hours after dosing. Serum was extracted by precipitation with an equal volume of acetonitrile containing 2 % formic acid followed by centrifugation. The supernatant was analyzed by liquid chromatography-mass spectrometry (ESI-MS) with a detection level of 0.03 to 3 µg/ml. Compounds **302** and **304a** showed detectable blood levels when administered orally, **214e** itself shows no blood levels above 0.10 µg/mL when administered orally. Compounds **302** and **304a** are prodrugs of **214e** and are metabolized to **214e** in vivo (see Fig. 11).

Example 9

We obtained the following data (see Tables 5 and 6) for compounds of this invention using the methods described in Examples 1-8. The structures of the compounds of Example 9 are shown in Example 10-17.

Table 5

Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
<b>47b</b>	27	1800	<600	338	
<b>47a</b>	19	2600	5100	79	32
<b>135a</b>	90	2800	5000	>100	

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Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
135b	320	1600	1700		
125b	60	800	4500		
108b	400	25000			>100
137	40	1700	14000		
139	350	2000			
213e	130	900	600 400*		
214c	1200	5000			
214e	7.5	1600	1300	23	12
217c		1700	7000	70	
217e		175	2000	>50	
220b	600	2125			
223b	99	5000		>100	
223e	1.6	3000	>20000	89	
226e	15	1100	1800	109	
227e	7	234	550		
230e		325	300	67	
232e	1100	4500		22	26
235e	510	4750		36	
238e	500	4250			
246	12	950	10000	31	
257	13	11000 6600*			
265	47	4300	1400	23	20
281	50	600 2500*			
302	4500	>20000	>20000		
304a	200	1,400	2400 14000*		
307a	55	14500	16000		
307b	165		14000		
404	2.9	1650 1800*	1100	64	24
405	6.5	1700	2100		
406	4	1650	2300		
407	0.4	540	1700		
408	0.5	1100	1000	41	23

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Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
409	3.7	2500			
410	17	2000	2800	32	20
411	0.9	540	1900		
412	1.3	580 660*	700 1000*		25
413	750	6200			
415	2.5	990 1000*	450 3500*	26	18
416	12	1200	3400		47
417	8	2000	6000	33	22
418	2.2	1050 2200*	7800 1800*	13	5.9
419	280	>8000			
420	1200	8000 >8000*			
421	200	4300 4600*			
422	50	2200	1200		
423	10	2100 1800*	1500		45
424	45	2500	4000		
425	0.8	650 700*	650		
426	90	4500 2500*			
427	180	4500			36
428	280				
429	7000				
430	60	>8000			
431	8	>8000	8000		
432	1.6	560	2000		
433	2.9	1000 1100*	1100		
434	4.9	1600 1200*	1800 1300*		20
435	8	4400			
436	7.5	2700			
437	12	1800	5000		

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Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
438	28	1000	700 2900*		22
439	3.7	2800	3200 3400*		
440	2.3	5000	2000		
441	1	2500	4500		
442	3.2	900	2000		54
443	3.6	2800	1500		
444	15	3500	3500		
445	135		4000		
446	62		3000		
447	5.8	2500	1500		
448	130		4000		
449	12	1500	3200 13000*		
450	5	800	2200 1700*	18	12
451	4	1800	1500 9000*		
452	4.5	600 800*	650 1600*		27.3
453	0.65	1300	1900 1600*		
454	45	2500			
455	1.2	400	2800 2600*		54
456	4.5	600 1300*	600 1400*		12.7
457	6.2	2000	3500		
458	20	2900			
459	5	1800			
460	115	400	2400		
461	47				
462	40				
463	14	2400 2800*			
464	2.5	1000	>1000 2500*		
465	3	1000	800		

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Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
466	0.8	1400	600		
467	11	1900			
468	4.5	850	2500		
470	5	500	360 500*		63
471	1	750	400		17
472	140				
473	1	1000	400 450*		
474	85				
475	5.5	690 650*	400 350*	31	21
476	7	1600	2500		
477	60				
478	380				
479	15	900	700 2400*		
480	25	2300			
481	1.2	390 930*	600 500*		34
482	<0.2	340	380 260*		
483	1.7	900	700		
484	2	1550 1400*	5000		15
485	2	900	900		
486	2.3	480 570*	500		37
487	2.4	650 950*	500 400*		20
488	1.5	940	750		
489	6	2250 1700*	15000		
490	4.3	980 1000*	700 1900*		
491	5	2500			
493	25	1200	800 850*		

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Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
494	15	1350 1500*	7000		
495	43				
496	16	1550 1600*	6000		
497	3.5	740	350 700*		
498	1.5	560	500 400*		
499	3.5	1200 800*	9000		
605a	90	2600	>20000		
605b	45	10000		97	
605c	615	4500		37	
605d	95	5100	16000 5100*	33	
605e	29	2250	>10000		24
605f	475	12500			
605g	165	22500			
605h	460	>25000			
605i	680	>20000			
605j	110	8750		71	
605m	650	20000			
605n	12	2100	>20000	28	
605o	72		18000		
605p	125	3200	>20000		
605q	1000				
605s	150	6000			
605t	33				
609a	114	>30000			
609b	27	>20000			
619	300				
620	35	1000	19000		
621	7.2	1300	>20000		
622	35	1300	>20000		
623	9				
624	300				



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	Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
	625	105				
	626	260				
	627	43	3250	8000		
	628	36	2750	>20000		
5	629	230				
	630	270				
	631	805				
	632	148				
	633	92	5750	20000		
10	634	1400				
	635	55	1900 3400*	4000		
	605v	1100	>30000			
	2201	9	2000 3700*	3500		60
	2100e	250	800	600		
15	2100a	100	1100	850		
	2002	4	810 860*	70 1400*		32
	2100d	>100000	>20000	>20000		
	2100c	7400	>20000	>20000		
	2100b	8000	>20000	>20000		
20	2001	135	1800	3500		
	1027	4000	>20000	>20000		60
	1015	40	2500	1700		23

Table 6

	Compound	Fluorescent Assay kinact $M^{-1} s^{-1}$	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
25	108a	$1 \times 10^5$	17500			
	136	$5.4 \times 10^5$	870	2800	93	

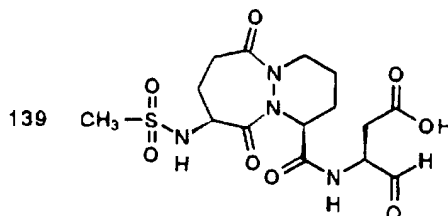
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Compound	Fluorescent Assay $k_{inact}$ $M^{-1} s^{-1}$	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
138	$1.2 \times 10^5$	900	2900	116	
217d	$4.7 \times 10^5$	340	4000		
280	$4 \times 10^5$	650	>1000		187
283	$1 \times 10^5$	<200	450		104
284	$3.5 \times 10^5$	470	550	77	100
285	$4.3 \times 10^5$	810	1000	130	50

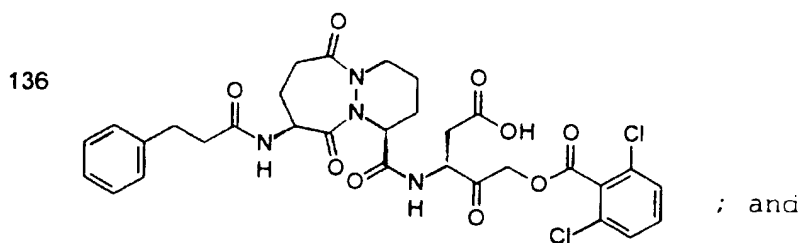
\* Values obtained upon reassay.

#### Example 10

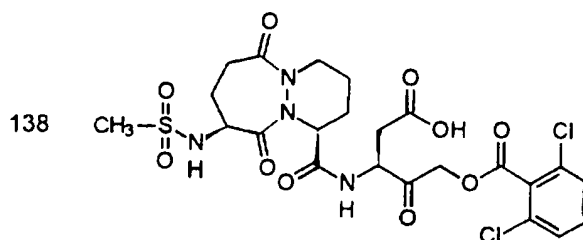
Compound 139 was synthesized by a method similar to the method used to synthesize 47a.



Compounds 136 and 138 were synthesized by a method similar to the method used to synthesize 57b.

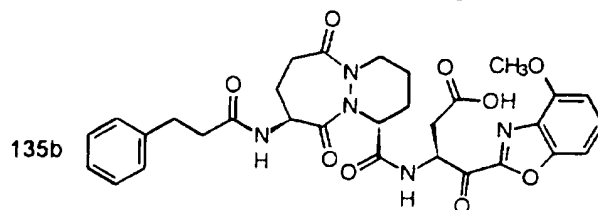
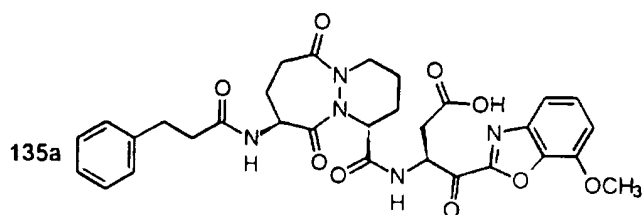


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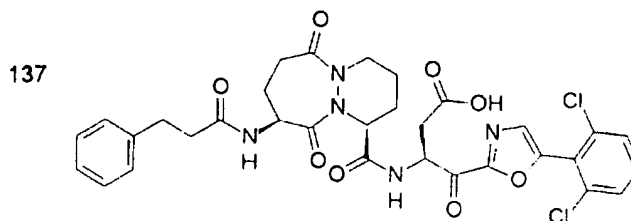


Compounds **135a**, **135b**, and **137** were synthesized by a method similar to the method used to synthesize **69a**.

5



; and



Compounds **813e**, **814c**, **814e**, **817c**, **817d**, **817e**,  
**820b**, **823b**, **823e**, **826e**, **827e**, **830e**, **832e**, **835e**, **838e**,  
 10 **846**, **857**, **865**, **902**, **904a**, **907a**, **907b**, **1004-1013**, **1015-**

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1045, 1046-1068, 1070-1091, and 1093-1099 were synthesized by methods similar to those used to synthesize compound 264 and the corresponding compounds in Examples 10 and 11.

5           Compounds 47a, 47b, 108a, 108b, 125b, 213e, 214c, 217c, 217d, 217e, 220b, 223b, 223e, 226e, 227e, 230e, 232e, 235e, 238e, 246, 257, 264, 265, 280-287, 302, 304a, 307a, and 307b were synthesized as described below.

10   H.   N-(N-Acetyl-tyrosinyl-valinyl-pipecolyl)-3-amino-4-oxobutanoic acid.

Step A.   N-(N-tert-Butoxycarbonylpipecolyl)-4-amino-5-benzyloxy-2-oxotetrahydrofuran.

Reaction of N-tert-butoxycarbonylpipecolic  
15   acid (460 mg, 2.0 mmol) and N-allyloxycarbonyl-4-amino-5-benzyloxy-2-oxotetrahydrofuran (530 mg, 1.82 mmol) was carried out by a method analogous to that reported by Chapman (Bioorg. & Med. Chem. Lett. 2, pp. 613-618, (1992)) to give 654 mg of the title compound.

20           <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub> (existing as rotamers)) δ 7.35 (m, 5H), 6.88 (br. s, 1H), 4.9-4.45(m, 4H), 3.95+ (br. m, 2H), 3.06 (m, 1H), 2.9 (m, 1H), 2.7 (br. m, 1H), 2.45 (m, 1H), 2.2 (m, 1H), 1.7-1.5 (m, 3H), 1.45 (two s, 9H).

25           Step B.   N-Pipecolyl-4-amino-5-benzyloxy-2-oxotetrahydrofuran.

N-(N-tert-Butoxycarbonylpipecolyl)-4-amino-5-benzyloxy-2-oxo-tetrahydrofuran (654 mg) was dissolved in 15 ml of 25% trifluoroacetic acid in dichloromethane

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and stirred at room temperature. The mixture was concentrated to give a gummy residue. The residue was dissolved in dichloromethane and washed with 10% sodium bicarbonate. The organic layer was dried over  
5 anhydrous sodium sulfate, filtered, and concentrated to give 422 mg of the title compound as a beige solid.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.38 (m, 5H), 7.15 (d, 1H), 5.55 (d, 1H), 4.95-4.8 (m, 1H), 4.78 (m, 1H), 4.65 (d, 1H), 4.45 (m, 1H), 3.2 (m, 0.5H), 3.05 (m, 0.5H), 2.95 (m, 0.5H), 2.85 (m, 0.5H), 2.65 (m, 1H), 2.55-2.38 (m, 1H), 1.95 (m, 1H), 1.8 (m, 1H), 1.6 (m, 2H), 1.38 (m, 2H).

Step C. N-(N-Acetyl-tyrosinyl-valinyl-pipecolyl)-4-amino-5-benzyloxy-2-oxo-tetrahydrofuran.  
15

N-Acetyl-tyrosinyl-valine (464 mg, 1.44 mmol) and N-Pipecolyl-4-amino-5-benzyloxy-2-oxotetrahydrofuran (412 mg, 1.3 mmol) were dissolved in 5 ml each of dimethylformamide and dichloromethane and  
20 cooled to 0°C. To the cooled solution was added 1-hydroxybenzotriazole (HOBT; 210 mg, 1.56 mmol) followed by the addition of 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC; 326 mg, 1.7 mmol). After stirring for 18 hours, the mixture was  
25 diluted with ethyl acetate and washed with water, 10% sodium hydrogen sulfate, 10% sodium bicarbonate, and water. The organic layer was concentrated to give a crude solid that was purified by flash chromatography ( $\text{SiO}_2$ ) eluting with 94:6:1

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(dichloromethane:isopropanol:pyridine) to give 370 mg of the title compound.

<sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD (existing as diastereomers as well as rotamers)) δ 7.35 (m, 5H),  
5 7.05 (m, 2H), 6.68 (m, 2H), 5.65 & 5.25 (m, 1H), 4.9-  
3.95 (m, 8H), 3.4-2.6 (m, 4H), 2.5-2.1 (m, 1H), 1.98  
(s, 1H), 1.9 (s, 1H), 1.85 (s, 1H), 1.8-1.6 (m, 2H),  
1.55-1.3 (m, 4H), 0.95-0.85 (m, 6H).

Step D. N-(N-Acetyl-tyrosinyl-valinyl-  
10 pipecolyl)-3-amino-4<sup>L</sup>-oxobutanoic acid.

To a solution of 100 mg of N-(N-Acetyl-  
tyrosinyl-valinyl-pipecolyl)-4-amino-5-benzyloxy-2-  
oxotetrahydrofuran in 10 ml of methanol was added 60 mg  
of Pd(OH)<sub>2</sub> on carbon and the mixture placed under an  
15 atmosphere of hydrogen via a balloon. The mixture was  
filtered through Celite and concentrated providing a  
white solid. This crude solid was dissolved in 2 ml of  
methanol and triturated with diethyl ether affording 26  
mg of the title compound.

20 <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD (existing as  
diastereomers as well as rotamers)) δ 7.1 (m, 2H), 6.7  
(m, 2H), 5.2 (br. m, 1H), 4.8-3.6 (m, 6H), 3.2-2.5 (m,  
4H), 2.5-2.1 (m, 1H), 1.95 (three s, 3H), 1.9-1.3 (m,  
6H), 1.1-0.7 (m, 6H).

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K. N-[N-Acetyl-tyrosinyl-valinyl-(4-benzyloxy)prolinyl]-3-amino-4-oxobutanoic acid.

5 Step A. N-(N-Allyloxycarbonyl-4-benzyloxyprolinyl)-3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone.

The title compound was prepared by the reaction of N-allyloxycarbonyl-4-benzyloxyproline and 3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone (T.L. Graybill et. al., Abstracts of  
10 papers, 206th National Meeting of the American Chemical Society, Abstract MEDI-235. Chicago, IL. (1993)) under similar peptide coupling conditions as reported above (compound H; Step C).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.05 (br. s, 1H),  
15 7.85 (br. m, 1H), 7.4-7.2 (m, 5H), 7.15 (br. s, 1H),  
6.55 (br. s, 1H), 5.9 (m, 1H), 5.1-4.9 (br. m, 2H),  
4.65-4.4 (m, 4H), 4.2 (br. m, 1H), 3.75-3.5 (m, 2H),  
2.75-2.55 (m, 2H), 2.5 (br. m, 1H), 2.25 (br. m, 1H)  
1.4 (s, 9H).

20 Step B. N-(N-Acetyl-tyrosinyl-valinyl-(4-benzyloxyprolinyl))-3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone.

The title compound was prepared by reaction of N-acetyl-tyrosinyl-valine and N-(N-allyloxycarbonyl-  
25 4-benzyloxyprolinyl)-3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone by reaction conditions reported for compound H, step A.

<sup>1</sup>H NMR (500MHz, CD<sub>3</sub>OD) δ 7.35-7.2 (m, 6H), 7.0  
(d, 2H), 6.65(d, 2H), 4.85 (m, 1H), 4.6-4.45 (m, 4H),  
30 4.3 (br. m, 1H), 4.15 (m, 1H), 3.7 (m, 1H), 2.95 (m,

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1H), 2.75-2.6 (m, 3H), 2.35 (m, 1H), 2.1 (m, 1H), 1.9 (s, 3H), 1.4 (s, 9H), 0.95 (d, 3H), 0.90 (s, 3H).

Step C. N-(N-Acetyl-tyrosinyl-valinyl-(4-benzyloxyprolinyl))-3-amino-4oxobutanoic acid.

5

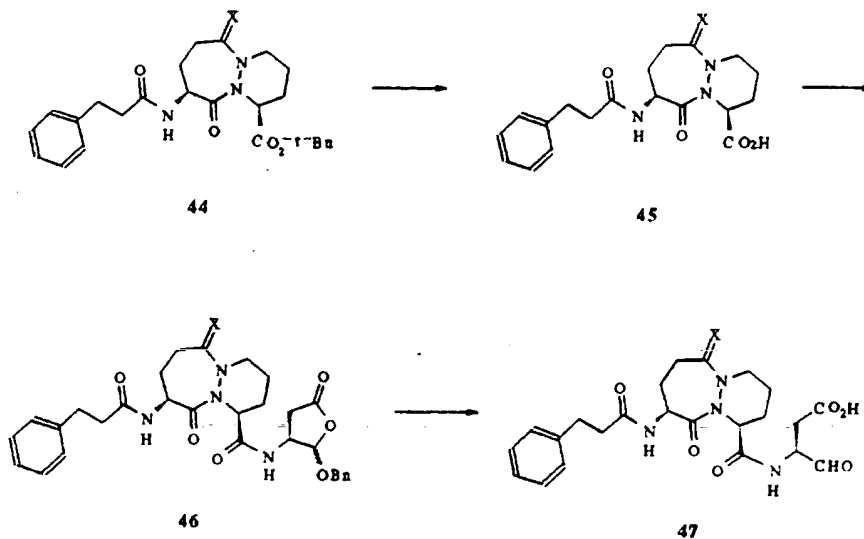
N-(N-Acetyl-tyrosinyl-valinyl-(4-benzyloxyprolinyl))-3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone (270 mg) was dissolved into 10 ml of 25% trifluoroacetic acid in dichloromethane and stirred at room temperature for 3 hours. The mixture was concentrated to give a solid residue. The residue was dissolved into a 10 ml mixture of methanol:acetic acid:37% formaldehyde (3:1:1) and stirred at room temperature for 1 hour. The mixture was concentrated and the resulting residue purified by flash chromatography (SiO<sub>2</sub>) eluting with dichloromethane/methanol/formic acid (100:5:0.5) to give 37 mg of the title compound.

<sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD (existing as a 1:1 mixture of diastereomers of the hemiacetal)) δ 7.4-7.25 (m, 5H), 7.0 (d, 2H), 6.65 (d, 2H), 4.65-4.05 (m, 7H), 3.75-3.4 (m, 2H), 3.05-2.3 (m, 5H), 2.2-1.95 (m, 2H), 1.90 (s, 3H), 1.0 (d, 3H), 0.95 (d, 3H).

20



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(a)  $X = O$ (b)  $X = H_2$ 

(1*S*,9*S*) t-Butyl 6,10-dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a]

- 5 [1,2]diazepine-1-carboxylate (44a). To a solution of (1*S*,9*S*)t-butyl 9-amino-6,10-dioxo-octahydro-6H-pyridazino [1,2-a][1,2]diazepine-1-carboxylate (690mg; 2.32mmol; GB 2128984) in dioxane (16ml) and water (4ml) at 0°C was added solid sodium bicarbonate (292mg; 3.48mmol) followed by dropwise addition of 3-phenylpropionyl chloride (470mg; 2.78mmol). The mixture was stirred at room temperature for 2h then more sodium bicarbonate (200mg; 2.38mmol) and 3-phenylpropionyl chloride (100mg; 0.6mmol) were added.
- 15 The mixture was stirred for a further 2h at room temperature, diluted with ethyl acetate (50ml), washed with saturated sodium bicarbonate (2 x 25ml) then dried ( $MgSO_4$ ) and concentrated. The residue was purified by flash chromatography (0-50% ethyl acetate/chloroform)

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and finally crystallized by trituration with ether to afford 860mg (86%) of a white solid: mp. 137-138°C;  $[\alpha]_D^{23}$  -95.1° (c 0.549, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3327, 1736, 1677, 1664, 1536, 1422, 1156; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.24

5 (5H, m), 6.50 (1H, d, J=7.5), 5.24 (1H, m), 4.90 (1H, m), 4.60 (1H, m), 3.44 (1H, m), 2.93 (2H, m), 2.84 (1H, m), 2.64 (1H, m), 2.54 (2H, m), 2.26 (2H, m), 1.70 (4H, m), 1.70 (9H, s). MS(FAB, m/z): 430 (M<sup>+</sup> + 1), 374, 242, 105, 91.

10 (1S,9S) t-Butyl octahydro-10-oxo-9-(3-phenylpropionylamino)-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxylate (44b), was prepared from (1S,9S) t-butyl 9-amino-octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (Attwood  
15 et al., J. Chem. Soc. Perkin 1, pp. 1011-19 (1986)) as for 44a, to afford 810mg (81%) of a colorless oil:  
 $[\alpha]_D^{23}$  - 33.5° (c 0.545, CH<sub>2</sub>Cl<sub>2</sub>); IR (film) 3334, 2935, 1737, 1728, 1659, 1642; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.24 (5H, m), 6.75 (1H, d, J=6.7), 5.27 (1H, m), 4.92 (1H, m), 3.39  
20 (1H, m), 3.03 (4H, m), 2.55 (3H, m), 2.33 (1H, m), 2.17 (1H, m), 1.80 (5H, m), 1.47 (9H, s), 1.39 (1H, m).  
MS(FAB, m/z): 416 (M<sup>+</sup> + 1), 360, 211, 143, 97.

(1S,9S) 6,10-Dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid (45a). To a solution  
25 of (1S,9S) t-butyl 6,10-dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (44a) (800mg; 1.863mmol) in dry dichloromethane (5ml) at 0°C was added  
30 trifluoroacetic acid (5ml). The solution was stirred at room temperature for 3h then concentrated. Dry

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ether (10ml) was added to the residue then removed under vacuum. This process was repeated three times to afford a crystalline solid. The solid was triturated with ether and filtered to afford 590mg (85%) of a  
5 white crystalline solid: mp. 196-197.5°C;  $[\alpha]_D^{23}$  -129.5° (c 0.2, CH<sub>3</sub>OH); IR (KBr) 3237, 1729, 1688, 1660, 1633, 1574, 1432, 1285, 1205; <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 8.28 (1H, d, J=7.4), 7.22 (5H, m), 5.32 (1H, dd, J=5.9, 2.9), 4.75 (1H, m), 4.51 (1H, m), 3.50 (1H, m), 3.01 (1H, m), 2.91  
10 (2H, m), 2.55 (2H, m), 2.29 (3H, m), 1.95 (2H, m), 1.71 (2H, m). Anal. Calcd for C<sub>19</sub>H<sub>23</sub>N<sub>3</sub>O<sub>5</sub>: C, 61.12; H, 6.21; N, 11.25. Found: C, 60.80; H, 6.28; N, 10.97. MS (FAB, m/z) 374 (M<sup>+</sup> + 1), 242, 105, 91.

(1S,9S) Octahydro-10-oxo-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a]-[1,2]diazepine-1-carboxylic acid  
15 (45b), was prepared from (1S,9S) t-butyl octahydro-10-oxo-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (44b) by the method described for compound 45a to afford 657mg  
20 (96%) of 45b as a crystalline solid: mp. 198-202°C;  $[\alpha]_D^{23}$  -86.2° (c 0.5, CH<sub>3</sub>OH); IR (KBr) 3294, 2939, 1729, 1645, 1620, 1574, 1453, 1214; <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.92 (1H, d, J=7.9), 7.20 (5H, m), 5.29 (1H, m), 4.90 (1H, m), 3.47 (1H, m), 3.08 (2H, m), 2.90 (2H, m), 2.55 (3H, m), 2.36 (1H, m), 1.81 (5H, m), 1.43 (2H, m). MS (FAB,  
25 m/z) 360 (M<sup>+</sup> + 1), 211, 143, 91.

[3S,2R,S,(1S,9S)] N-(2-Benzoyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (46a).  
30 To a solution of (1S,9S) 6,10-dioxo-octahydro-9-(3-phenyl-propionylamino)-6H-pyridazino[1,2-a]

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[1,2]diazepine-1-carboxylic acid (**45a**) (662mg; 1.773mmol) in dry dichloromethane (9ml) and dry dimethyl formamide (3ml) at room temperature was added bis(triphenylphosphine)palladium chloride (30mg) and

5 (3*S*,2*R*,*S*)-3-allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydrofuran (Chapman, Bioorg. Med. Chem. Lett., 2, pp. 613-18 (1992)) (568mg; 1.95mmol) followed by dropwise addition of tri-*n*-butyltin hydride (1.19g; 4.09mmol). 1-Hydroxy-benzotriazole (479mg; 3.546mmol)

10 was added to the mixture and the mixture was cooled to 0°C before addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (408mg; 2.128mmol). The mixture was stirred at room temperature for 3.25h then diluted with ethyl acetate (50ml), washed twice

15 with dilute hydrochloric acid (20ml), twice with saturated sodium bicarbonate (20ml), once with brine then dried (MgSO<sub>4</sub>) and concentrated. The resulting oil was purified by flash chromatography (0-100% ethyl acetate/chloroform) to afford 810mg (81%) of **46a** as a

20 mixture of anomers: mp. 92-94°C; IR (KBr) 3311, 1791, 1659, 1651, 1536; <sup>1</sup>H NMR(CDCl<sub>3</sub>) δ 7.49, 6.56 (1H, 2d, *J*=6.7, 7.8), 7.29 (10H, m), 6.37, 6.18 (1H, 2d, *J*=7.7, 7.6), 5.56, 5.34 (1H, d, s, *J*=5.2), 5.08-4.47 (6H), 3.18-2.80 (5H), 2.62-2.28 (5H), 2.04-1.53 (5H).

25 MS(FAB, *m/z*), 563 (*M*<sup>+</sup> + 1), 328, 149, 91.

[3*S*,2*R*,*S*,(1*S*,9*S*)] *N*-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-octahydro-10-oxo-9-(3-phenylpropionylamino)-6*H*-pyridazino[1,2-*a*]

[1,2]diazepine-1-carboxamide (**46b**), was prepared from

30 **45b** by the method described for **46a** to yield 790mg (96%) of a glass: m.p. 58-60°C; IR (KBr) 3316, 2940, 1793, 1678, 1641, 1523, 1453, 1120; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ

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7.28 (10H, m), 6.52, 6.42 (1H, 2d,  $J=7.2$ , 7.1), 5.53, 5.44 (1H, d, s,  $J=5.2$ ), 5.35 (1H, m), 4.6-4.9, 4.34 (4H, m), 3.1-2.8 (6H, m), 2.6-2.1 (7H), 1.95-1.05 (5H). MS (FAB,  $m/z$ ), 549 ( $M^+ + 1$ ), 400, 310, 279, 91.

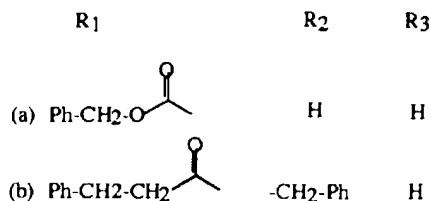
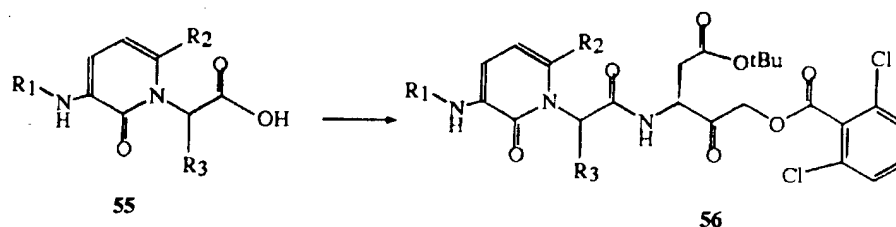
- 5 [3S(1S,9S)] 3-(6,10-Dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (47a).

A mixture of [3S, 2R,S, (1S,9S)] N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (46a) (205mg; 0.364mmol), 10% palladium on carbon (200mg) and methanol (20ml) was stirred under hydrogen at atmospheric pressure for 5h. The mixture was filtered then concentrated to yield 154mg (90%) of a glass: mp. 116-118°C;  $[\alpha]_D^{23}$  -140° (c 0.1, CH<sub>3</sub>OH); IR (KBr) 3323 (br), 1783, 1731, 1658, 1539, 1455, 1425; <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  7.21 (5H, m), 5.17 (1H, m), 4.73 (1H, m), 4.50 (2H, m), 4.23 (1H, m), 3.38 (1H, m), 3.06 (1H, m), 2.91 (2H, m), 2.73-2.18 (6H, m) and 2.01-1.59 (5H, m). Anal. Calcd for C<sub>23</sub>H<sub>27</sub>N<sub>4</sub>O<sub>7</sub> + H<sub>2</sub>O : C, 56.32; H, 6.16; N, 11.42. Found: C, 56.29; H, 6.11; N, 11.25. MS (FAB,  $m/z$ ) 473 ( $M^+ + 1$ ), 176, 149, 105, 91.

- [3S(1S,9S)] 3-(Octahydro-10-oxo-9-(3-phenylpropionylamino)-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (47b), was prepared from 46b by the method described for 47a. The residue was purified by flash chromatography (0-10% methanol/chloroform) to afford 65mg (52%) of a glass; mp. 87-90°C;  $[\alpha]_D^{23}$  -167.0° (c 0.1, methanol); IR (KBr) 3329, 2936, 1786, 1727, 1637; <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$

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7.23 (5H, m), 5.29 (1H, m), 4.83 (1H, m), 4.59 (1H, d,  $J=3.6$ ), 4.29 (1H, m), 3.3-3.0 (3H, m), 2.91 (2H, m), 2.70-2.34 (5H, m), 2.19 (2H, m), 1.75 (4H, m), 1.36 (2H, m). Anal. Calcd for  $C_{23}H_{30}N_4O_6 + 0.5H_2O$ : C, 59.09; H, 6.68; N, 11.98. Found: C, 58.97; 6.68; N, 11.73. MS (FAB,  $m/z$ ) 459 ( $M^+ + 1$ ), 310, 149, 105, 91.



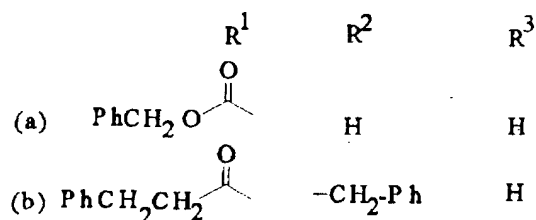
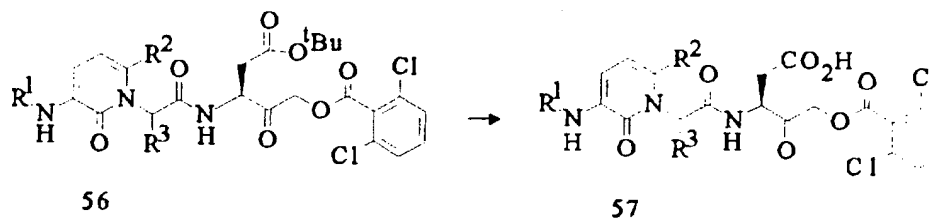
t-Butyl N-2-(3-benzyloxycarbonylamino-1,2-dihydro-2-oxo-1-pyridyl)acetyl-3-amino-5-(2,6-dichlorobenzoyloxy)-4-oxopentanoate (56a). The acetic acid (55a) (WO 93 21213) in THF (2ml) was stirred at room temperature and treated with 1-hydroxybenzotriazole (60mg, 0.448mmol) and dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (47mg, 0.246mmol). After 5 mins water (2 drops) was added and stirring continued for 20 minutes. Bis(triphenylphosphine) palladium II chloride (6mg) was added followed by a solution of t-butyl 3-(allyloxycarbonylamino)-4-oxo-5-(2,6-dichlorobenzoyl-oxy)pentanoate (WO 93 16710) (103mg, 0.224mmol) in THF (1ml). Tributyltin hydride

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(0.09ml, 0.336mmol) was added dropwise over 1 hour at room temperature. The mixture was stirred for a further 3 hours and poured onto ethyl acetate, washed with 1M HCl, aqueous NaHCO<sub>3</sub>, brine, dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was triturated with pentane and the supernatant discarded. The remaining solid was purified by flash chromatography (50% ethyl acetate/hexane) to afford the title compound 92mg (63%) as a colorless oil:  $[\alpha]_D^{26} -29.6^\circ$  (c 1.1, CH<sub>2</sub>Cl<sub>2</sub>); IR (film) 3377, 3365, 3332, 3312, 1733, 1691, 1650, 1599, 1515, 1366, 1261, 1153, 1068, 747; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  8.09 (1H, d, *J* = 6.8), 7.84 (1H, s), 7.58 (1H, d, *J* = 8.3), 7.33 (8H, m), 7.02 (1H, dd, *J* = 6.9, 1.7), 6.33 (1H, t, *J* = 7.2), 5.20 (2H, s), 5.12 (2H, m), 4.89 (1H, dt), 4.65 (2H, m), 2.80 (2H, m), 1.38 (9H, s).

**t-Butyl N-2-(6-benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl)acetyl-3-amino-5-(2,6-dichlorobenzyloxy)-4-oxo-pentanoate (56b)**, was prepared by the method described for (56a) which afforded the title compound (66%) as a colorless oil: IR (film) 3364, 3313, 1738, 1688, 1648, 1600, 1566, 1514, 1433, 1369, 1254, 1152; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  8.40 (1H, d, *J* 7.6), 8.30 (1H, s), 7.28 (13H, m), 6.20 (1H, d, *J* = 7.6), 5.12 (2H, q), 4.86 (1H, m), 4.65 (2H, q), 4.06 (2H, s), 3.07-2.61 (6H, m), 1.39 (9H, s).

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N-2(3-Benzoyloxycarbonylamino-1,2-dihydro-2-oxo-1-pyridyl)acetyl-3-amino-5-(2,6-dichlorobenzoyloxy)-4-oxo-pentanoic acid (57a; Q). The ester 56a (210mg, 0.356mmol) in dichloromethane (0.5ml) was cooled to 0°C and treated with trifluoroacetic acid (0.5ml), stirred and warmed to 20°C over 30 minutes. The solution was evaporated to dryness under reduced pressure, redissolved in dichloromethane and concentrated (x3). The residue was triturated with ethyl acetate and diluted with ether to afford the title compound 162mg (85%) as a colorless solid: m.p. 165-8°C (decomposition);  $[\alpha]_D^{23}$  -38.8° (c 0.1, CH<sub>3</sub>OH); IR (KBr) 3332, 3275, 1723, 1658, 1649, 1597, 1581, 1562, 1526, 1432, 1385, 1258, 1218, 1206; <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ 8.96 (1H, d, J = 7.3), 8.34 (1H, s), 7.85 (1H, dd, J = 7.3), 7.58 (3H, m), 7.35 (5H, m), 6.29 (1H, t, J = 7.3), 5.26 (2H, m), 5.15 (2H, s), 4.69 (3H, m), 2.75 (2H, m). Anal. Calcd. C<sub>27</sub>H<sub>23</sub>N<sub>3</sub>O<sub>9</sub>Cl<sub>2</sub>: C, 53.66; H, 3.84; N, 6.95. Found: C, 53.36; H, 3.90; N, 6.81. M.S. (+ FAB); 604 (M<sup>+</sup> + 1), 285, 241, 195, 173, 149, 91.



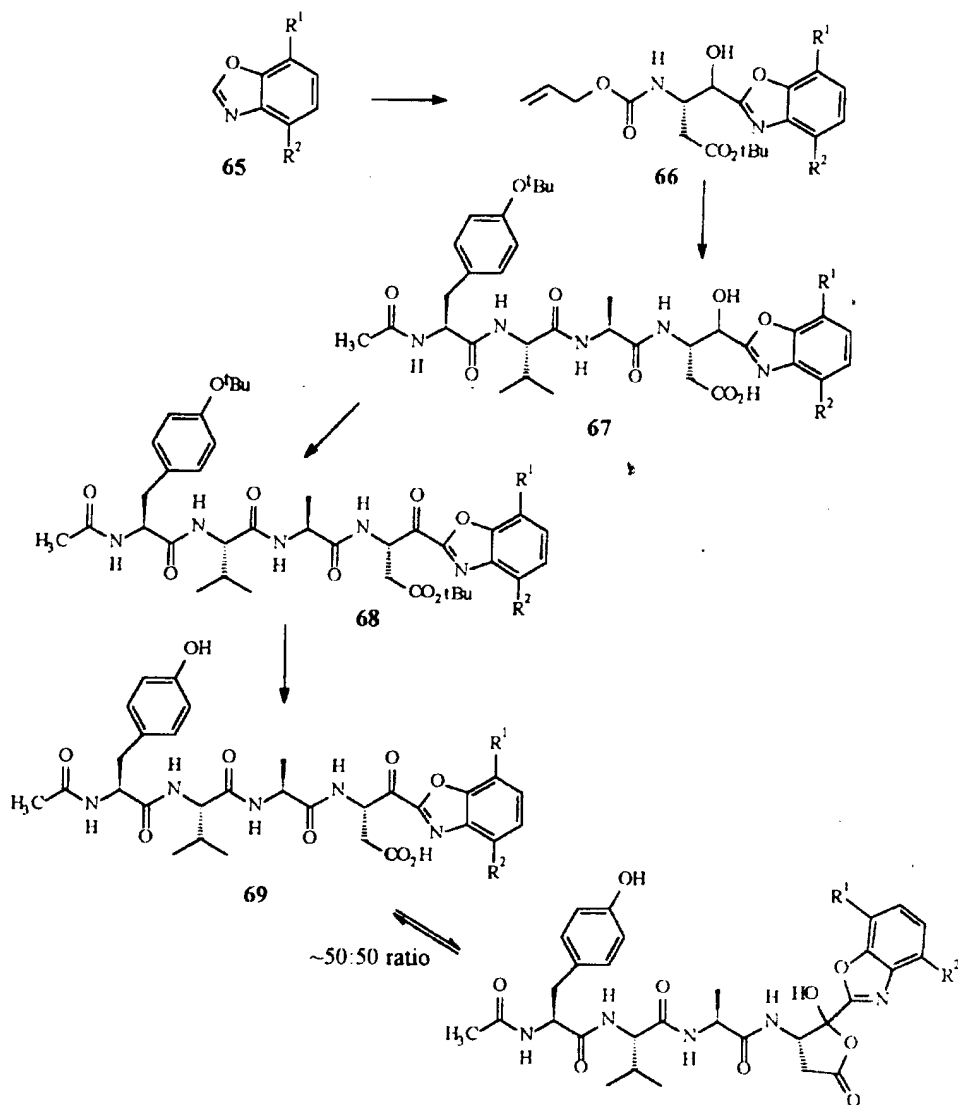
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N-2-(6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)  
amino-1-pyridyl)acetyl-3-amino-5-(2,6-dichloro-  
benzoyloxy)-4-oxo-pentanoic acid (57b; P), was prepared  
by the method described for 57a which afforded the

5 title compound (78%) as colorless crystals: m.p. 116-  
120°C (decomposition);  $[\alpha]_D^{26} -41.1^\circ$  (c 0.1, CH<sub>3</sub>OH); IR  
(KBr) 3299, 1739, 1715, 1689, 1666, 1645, 1598, 1563,  
1518, 1432, 1209, 1151; <sup>1</sup>H NMR (d<sub>6</sub>-DMSO)  $\delta$  9.24 (1H,  
s), 8.88 (1H, d,  $J = 7.6$ ), 8.18 (1H, d,  $J = 7.7$ ), 7.60  
10 (3H, m), 7.26 (10H, m), 6.06 (1H, d,  $J = 7.7$ ), 5.23  
(2H, ABq), 4.69 (3H, m), 3.93 (2H, s), 2.78 (6H, m).

Anal. Calcd. for C<sub>35</sub>H<sub>31</sub>N<sub>3</sub>O<sub>8</sub>Cl<sub>2</sub> · H<sub>2</sub>O: C, 59.16; H, 4.68;  
N, 5.91. Found: C, 59.38; H, 4.53; N, 5.84. M.S. (+  
FAB); 694, (Cl=35, 37), (M<sup>+</sup> + 1); 692 (Cl=35, 35), (M<sup>+</sup>  
15 + 1).

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(a)  $R^1 = \text{OCH}_3$ ,  $R^2 = \text{H}$ (b)  $R^1 = \text{H}$ ,  $R^2 = \text{OCH}_3$ 

**7-Methoxybenzoxazole (65a).** A mixture of 2-nitro-6-methoxyphenol (2.62g, 15.5mmol) (EP 333176) and 10% Palladium on carbon (130mg) in ethanol (50.0ml) was stirred under an atmosphere of  $\text{H}_2$  for 75min. The

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mixture was filtered through Celite® then immediately treated with *p*-toluenesulphonic acid (32.0mg) and triethylorthoformate (6.45ml, 38.8mmol) then heated under reflux under an atmosphere of N<sub>2</sub>. After 20h *p*-toluenesulphonic acid (30.0mg) and triethylorthoformate (6.45ml, 38.8mmol) were added. After a total of 44h heating, the reaction was allowed to cool and reduced *in vacuo*. The resulting residue was purified by flash chromatography (25:75 ethyl acetate/hexane) to give 1.97g (85%) of the title compound as a yellow solid: m.p. 28-31°C; IR (film) 1629, 1497, 1434, 1285, 1097; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.09 (1H, s), 7.40 (1H, d, *J* = 8.0), 7.28 (1H, t, *J* = 8.0), 6.89 (1H, d, *J* = 8.0), 4.02 (3H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 152.84, 145.82, 142.50, 139.99, 125.75, 113.42, 108.80, 56.97. Anal. Calcd. for C<sub>8</sub>H<sub>7</sub>N<sub>1</sub>O<sub>2</sub> · 0.1H<sub>2</sub>O: C, 63.65; H, 4.81; N, 9.29. Found: C, 63.43, H, 4.88, N, 9.05. M.S. (+ FAB); 150 (M<sup>+</sup> + 1).

**4-Methoxybenzoxazole (65b).** To a suspension of 4-hydroxybenzoxazole (2.00g, 14.8mmol) (Musser et al., J. Med. Chem., 30, pp. 62-67 (1987)) in acetone (80.0ml) was added dried K<sub>2</sub>CO<sub>3</sub> (2.25g, 16.3mmol) followed by iodomethane (1.38ml, 22.2mmol). The reaction was heated under reflux under N<sub>2</sub> for 4.5h, then filtered and reduced *in vacuo* to afford the crude product. The resulting residue was purified by flash chromatography (25:75 ethyl acetate/hexane) to give 2.0g (91%) of the title compound as a white crystalline solid: m.p. 72-74°C; IR (KBr) 3089, 1619, 1610, 1503, 1496, 1322, 1275, 1090, 1071, 780, 741; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.02 (1H, s), 7.32 (1H, t, *J* = 8.0), 7.18 (1H, d, *J* = 8.0), 6.81 (1H, d, *J* = 8.0), 4.04 (3H, s). Anal. Calcd. for

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C<sub>8</sub>H<sub>7</sub>NO<sub>2</sub>: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.40; H, 4.84; N, 9.31; m/z (EI) 149 (M<sup>+</sup> + 1, 100%).

**(3S, 4R,S) t-Butyl N-(allyloxycarbonyl)-3-amino-4-hydroxy-4-(2-(7-methoxybenzoxazolyl))butanoate (66a).**

- 5 To a stirred solution of 7-methoxybenzoxazole **65a** (548.6mg, 3.68mmol) in anhydrous THF (18.5ml) at -78°C under N<sub>2</sub> was added 1.56M *n*-butyl lithium in hexanes (2.47ml, 3.86mmol) dropwise, to produce a yellow colored solution. After stirring at -78°C for 20 min,
- 10 dry MgBr<sub>2</sub>OEt<sub>2</sub> (1.045g, 4.05mmol) was added as a solid. The resulting heterogeneous mixture was warmed to -45°C and stirred for 15min. The reaction mixture was then recooled to -78°C and a solution of (S)-Alloc-Asp(*t*-Bu)H (946.4mg, 3.68mmol) in THF (18.5ml) was added
- 15 dropwise. The reaction was stirred at -78°C for 30min, warmed to 0°C and stirred for 1h. The resulting homogeneous reaction was warmed to room temperature and stirred for 16h. The reaction was quenched with 5% sodium bicarbonate (3.5ml) then THF was removed *in*
- 20 *vacuo*. The resulting aqueous residue was extracted with methylene chloride (x6). The combined extracts were washed with brine, dried (MgSO<sub>4</sub>), filtered and reduced *in vacuo* to give 1.8g of crude product. Flash chromatography (40:60 ethyl acetate/hexane) gave 1.21g
- 25 (81%) of the title compound, an oil, as a mixture of diastereoisomers at C-4: IR (CH<sub>2</sub>Cl<sub>2</sub>) 3425, 2983, 1725, 1504, 1290, 1157, 1101; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.35-7.19 (2H, m), 6.89-6.81 (1H, m), 6.00-5.57 (2H, m), 5.32-5.05 (3H, m), 4.68-4.35 (3H, m), 4.01 (3H, s), 2.86-2.59 (2H, m), 1.45 (9H, s), 1.41 (9H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ
- 30 171.18, 171.09, 165.80, 165.30, 156.71, 156.60, 145.65, 142.76, 142.71, 140.82, 140.72, 133.23, 125.81, 125.72,

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118.41, 118.21, 113.07, 112.87, 108.95, 82.16, 70.28, 69.98, 66.52, 66.39, 57.03, 52.57, 52.29, 37.83, 36.86, 28.65. Anal. Calcd. for  $C_{20}H_{26}N_2O_7 \cdot 0.6H_2O$ : C, 57.57; H, 6.57; N, 6.72. Found: C, 57.49, H, 6.34, N, 6.60.  
5 M.S. (+ FAB); 407 ( $M^+ + 1$ ); 351, 307, 154.

(3*S*, 4*R*,*S*) t-Butyl N-(allyloxycarbonyl)-3-amino-4-hydroxy-4-(2-(4-methoxybenzoxazolyl))butanoate (66b), was prepared according to the method described for 66a which afforded 1.29g (26%, 68% based on recovered  
10 starting material) of the title compound as an oil and as a mixture of diastereoisomers at C-4: IR ( $CH_2Cl_2$ ) 3400, 1725, 1625, 1505, 1369, 1354, 1281, 1263, 1226, 1158, 1092, 1048;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.34-7.24 (1H, m), 7.16 (1H, d,  $J = 8.2$ ), 6.79 (1H, d,  $J = 7.9$ ), 6.00-5.50  
15 (2H, m), 5.30-5.05 (3H, m), 4.70-4.35 (4H, m), 4.02 (3H, s), 2.90-2.45 (2H, m), 1.45-1.41 (9H, 2 x s).  
Anal. Calcd. for  $C_{20}H_{26}N_2O_7 \cdot 0.4H_2O$ : C, 58.07; H, 6.53; N, 6.77. Found: C, 58.09; H, 6.41; N, 6.63.  
M.S. (+ FAB); 407 ( $M^+ + 1$ , 88%); 351 (100).

20 (3*S*, 4*R*,*S*) t-Butyl N-(N-acetyl-(*S*)-(O-tert-butyl-tyrosinyl)-(*S*)-valinyl-(*S*)-alaninyl)-3-amino-4-hydroxy-4-(2-(7-methoxybenzoxazolyl))butanoate (67a). To a stirred solution of the benzoxazole 66a (481.9mg, 1.19mmol) and Ac-Tyr(<sup>t</sup>Bu)-Val-Ala-OH (586.3mg, 1.30mmol) in methylene chloride (3.5ml) and DMF (3.5ml)  
25 was added bis(triphenylphosphine) palladium (II) chloride (18.0mg), followed by tributyltinhydride (0.80ml, 2.96mmol) dropwise. Hydroxybenzotriazole (320.4mg, 2.37mmol) was added and the mixture cooled to  
30 0°C. 1-Ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (278.2mg, 1.42mmol) was added and the

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mixture was allowed to warm to room temperature and stirred for 16.5h. The reaction was diluted with ethyl acetate and washed twice with 1M sodium hydrogensulphate, twice with saturated sodium bicarbonate, water, and brine. The organic layer was dried (MgSO<sub>4</sub>), filtered and reduced *in vacuo* to yield 2.0g of crude product. Flash chromatography (95:5 methylene chloride/methanol) gave 844.0mg (94%) of the title compound as a white solid: m.p. 205°C; IR (KBr) 3399, 3304, 2977, 1729, 1643, 1506, 1367, 1290, 1161; <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ 8.24-7.78 (4H, m), 7.43-7.32 (2H, m), 7.23 (2H, d, *J* = 8.5), 7.16-7.07 (1H, m), 6.93 (2H, d, *J* = 8.5), 6.52, 6.40 (1H, 2 x d, *J* = 5.5, *J* = 5.0), 5.03, 4.78-4.49, 4.45-4.16 (5H, brt, 2 x m), 4.05, 4.04 (3H, 2 x s), 3.08-2.35 (14H, m), 2.11-1.89 (1H, m), 1.83 (3H, s), 1.49-1.32, 1.15, 1.0-0.81 (27H, s, 2 x m, *J* = 7.0); <sup>13</sup>C NMR (d<sub>6</sub>-DMSO) δ 175.55, 175.18, 173.88, 173.75, 173.05, 169.23, 157.28, 148.55, 146.16, 143.21, 136.63, 133.55, 128.87, 127.17, 115.78, 111.92, 84.02, 81.50, 71.40, 61.15, 60.05, 57.79, 53.39, 51.62, 43.76, 40.52, 34.58, 32.52, 31.60, 26.35, 23.11, 22.71, 21.76. Anal. Calcd. for C<sub>39</sub>H<sub>55</sub>N<sub>5</sub>O<sub>10</sub> · 0.5H<sub>2</sub>O: C, 61.40; H, 7.40; N, 9.18. Found: C, 61.43; H, 7.31; N, 9.07. M.S. (+ FAB); 754 (M<sup>+</sup> + 1); 698, 338, 267.

(3*S*, 4*R*, *S*) *t*-Butyl N-(N-acetyl-(*S*)-(O-*tert*-butyl-tyrosinyl)-(*S*)-valinyl-(*S*)-alaninyl)-3-amino-4-hydroxy-4-(2-(4-methoxybenzoxazolyl))butanoate (67b), was prepared according to the method described for 67a which afforded 1.05g (94%) of the title compound as a fine white powder: m.p. 210-213°C (dec); IR (KBr) 3284, 2977, 1736, 1691, 1632, 1536, 1505, 1452, 1392, 1367, 1258, 1236, 1161, 1091; <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ 8.20-

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7.75 (4H, m), 7.40-7.10 (4H, m), 7.00-6.80 (3H, m), 6.45, 6.34 (1H, 2 x d,  $J = 5.3$ ,  $J = 5.0$ ), 5.00-4.10 (5H, m), 4.00, 3.99 (3H, 2 x s), 3.00-2.25 (4H, m), 1.95 (1H, m), 1.78 (3H, s), 1.39-0.80 (27H, m). Anal.

5 Calcd. for  $C_{39}H_{55}N_5O_{10}$ .  $0.5H_2O$ : C, 61.40; H, 7.40; N, 9.18. Found: C, 61.58; H, 7.38; N, 8.91. M.S. (+ FAB); 754 ( $M^+ + 1$ , 30%); 72 (100).

(3S) t-Butyl N-(N-acetyl-(S)-(O-tert-butyl-tyrosinyl)-(S)-valinyl-(S)-alaninyl)-3-amino-4-(2-(7-methoxybenzoxazolyl))-4-oxobutanoate (68a). The Dess-Martin reagent (1.082g, 2.55mmol) (Ireland et al., J. Org. Chem., 58, p. 2899 (1993); Dess et al., J. Org. Chem., 48, pp. 4155-4156 (1983)) was added to a stirred suspension of the alcohol 67a (641.0mg, 0.85mmol) in 15 methylene chloride (46.0ml). The resulting mixture was stirred for 1h before being partitioned between saturated sodium thiosulphate: saturated sodium bicarbonate (1:1, 86.0ml) and ethyl acetate (86.0ml). The resultant organic phase was washed in turn with 20 saturated sodium thiosulphate: saturated sodium bicarbonate (1:1), saturated sodium bicarbonate, and brine. The organic phase was dried ( $MgSO_4$ ), filtered and reduced in vacuo to give 660.0mg of crude product. Flash chromatography (94:6 methylene chloride/methanol) 25 gave 636.0mg (100%) of the title compound as a white solid: m.p. 209°C;  $[\alpha]_D^{24} -21.8^\circ$  (c 0.16, methanol); IR (KBr) 3395, 3294, 2977, 1722, 1641, 1535, 1505, 1161;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  8.43-8.16 (1H, m), 7.97-7.62 (2H, m), 7.49-7.14 (3H, m), 7.08-6.95 (3H, m), 6.89-6.73 (2H, 30 m), 5.81-5.68 (1H, m), 5.16-4.86 (2H, m), 4.53 (1H, brt), 4.03 (3H, s), 3.16-2.84 (4H, m), 2.11-1.84 (4H, m), 1.46-1.14 (21H, m), 0.92-0.78 (6H, m);  $^{13}C$  NMR

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(CDCl<sub>3</sub>)  $\delta$  186.28, 173.39, 171.90, 171.19, 171.03, 169.89, 156.43, 154.75, 146.32, 142.88, 140.98, 132.31, 130.54, 126.98, 124.73, 114.95, 111.42, 82.44, 78.71, 58.92, 57.20, 54.91, 53.47, 48.77, 39.43, 38.15, 32.79, 29.44, 28.60, 23.55, 20.27, 19.70, 19.34. M.S. (+ FAB); 752 ( $M^+ + 1$ ); 696, 336, 265.

**(3S) t-Butyl N-(N-acetyl-(S)-(O)-tert-butyl-tyrosinyl)-(S)-valinyl-(S)-alaninyl)-3-amino-4-(2-(4-methoxybenzoxazolyl))-4-oxobutanoate (68b)**, was

10 prepared according to the method described for the ketone **68a** which afforded 420mg (55%) of the title compound as a white solid: m.p. 211-213°C (dec);  $[\alpha]_D^{24}$  -23.9° (c 0.82, methanol); IR (KBr) 3277, 3075, 1723, 1690, 1632, 1530, 1506, 1392, 1366, 1269, 1234, 1160, 1094; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  8.15 (1H, brs), 7.7 (2H, brs), 7.46 (1H, t,  $J = 8.3$ ), 7.24 (2H, d,  $J = 8.3$ ), 7.10 (1H, brs), 7.03 (2H, d,  $J = 8.3$ ), 6.83 (3H, m), 5.74 (1H, q,  $J = 6.9$ ), 5.00 (2H, m), 4.51 (1H, t,  $J = 7.0$ ), 4.07 (3H, s), 3.20-2.95 (4H, m), 2.00 (4H, m), 1.42 (3H, d,  $J = 6.8$ ), 1.35 (9H, s), 1.23 (9H, s), 0.86 (6H, d,  $J = 6.7$ ). M.S. (+ FAB); 752 ( $M^+ + 1$ , 7%); 72 (100).

**(3S) N-(N-Acetyl-(S)-tyrosinyl-(S)-valinyl-(S)-alaninyl)-3-amino-4-(2-(7-methoxybenzoxazolyl))-4-oxobutanoate (69a; R)**. A solution of the ester **68a** 25 (600.0mg, 0.80mmol) in a 1:1 mixture of methylene chloride and trifluoroacetic acid (65.0ml) was stirred for 1h under a dry atmosphere of N<sub>2</sub>. The solution was then reduced in vacuo, taken up in ether and reduced again. This process was repeated six times to afford 30 the crude product as an off white solid. Flash chromatography (gradient 95:5 to 80:20 methylene



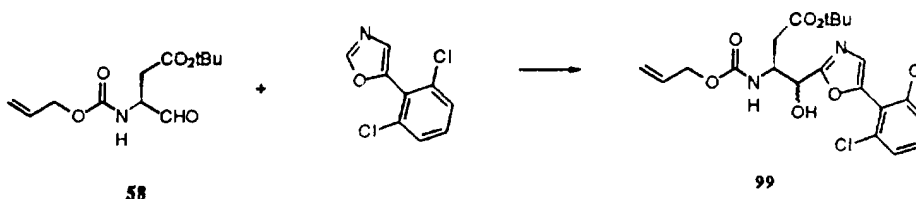
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chloride/methanol) gave 420.8mg (83%) of the title compound as a hygroscopic white solid. The product existed as a mixture of three isomers in CD<sub>3</sub>OD, consisting of the keto form (c 50%), and its acycloxy keto form (two isomers at C-4, c 50%): m.p. decomposes above 150°C;  $[\alpha]_D^{24}$ -33.2° (c 0.17, methanol); IR (KBr) 3300, 1715, 1658, 1650, 1531, 1517, 1204; <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.46-7.19 (2H, m), 7.16-6.91 (3H, m), 6.70-6.59 (2H, m), 5.62-5.49 (1H, m), 5.00-4.72 (1H, obscured m), 4.69-4.51 (1H, m), 4.49-4.08 (2H, m), 4.05-3.89 (3H, m), 3.16-2.47 (4H, m), 2.05-1.78 (4H, m), 1.41-1.11, 1.05-0.70 (9H, 2 x m). Anal. Calcd. for C<sub>31</sub>H<sub>37</sub>N<sub>5</sub>O<sub>10</sub> · 3H<sub>2</sub>O: C, 53.67; H, 6.25; N, 10.10. Found: C, 53.76; H, 5.56; N, 10.28. M.S. (+ FAB); 640 (M<sup>+</sup> + 1); 435, 147.

**(3S) t-Butyl N-(N-acetyl-(S)-tyrosinyl-(S)-valinyl-(S)-alaninyl)-3-amino-4-(2-(4-methoxybenzoxazolyl))-4-oxobutanoate (69b; S)**, was prepared according to the method described for the acid **69a** which afforded the hygroscopic title compound 252mg (96%). The product existed as a mixture of three isomers in CD<sub>3</sub>OD, consisting of the keto form, and its acycloxy ketal form (two isomers at C-4). The product existed as a single isomer in d-6 DMSO: m.p. 200-203°C (dec.);  $[\alpha]_D^{24}$  -38.0° (c 0.23, methanol); IR (KBr) 3289, 2968, 1718, 1713, 1658, 1634, 1548, 1517, 1506, 1461, 1453, 1393, 1369, 1268, 1228, 1174, 1092; <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ 9.20 (1H, brs), 8.71 (1H, d, J = 6.2), 8.10 (2H, m), 7.83 (1H, d, J = 8.7), 7.61 (1H, t, J = 8.2), 7.46 (1H, d, J = 8.2), 7.08 (3H, m), 6.65 (2H, d, J = 8.3), 5.50 (1H, q, J = 6.5), 4.50 (1H, m), 4.37 (1H, m), 4.20 (1H, m), 4.05 (3H, s), 3.09-2.77 (4H, m), 1.94 (1H, m), 1.79

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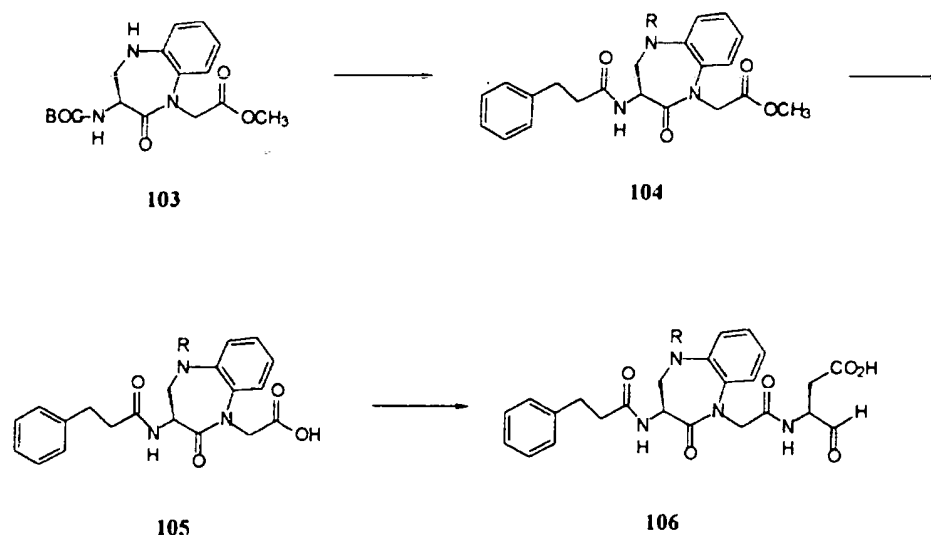
(3H, s), 1.23 (3H, d,  $J = 7.0$ ), 0.82 (6H, m). Anal. Calcd. for  $C_{31}H_{37}N_5O_{10}$ .  $1.5H_2O$ : C, 55.85; H, 6.05; N, 10.51. Found: C, 55.21; H, 5.69; N, 10.13. M.S. (+ FAB); 640 ( $M^+ + 1$ , 22%); 107 (100).



- 5 **3(S)-(Allyloxycarbonyl)-amino-4-[(2,6-dichloro-phenyl)-oxazol-2-yl]-4(R,S)-hydroxy-butyric acid tert-butyl ester (99).** A solution of 5-(2,6-Dichlorophenyl)oxazole (2.71g, 12.7mmol; prepared by a similar method described in Tet. Lett. 23, p. 2369
- 10 (1972)) in tetrahydrofuran (65mL) was cooled to  $-78^{\circ}\text{C}$  under a nitrogen atmosphere. To this solution was added n-butyl lithium (1.5M solution in hexanes, 8.5mL, 13.3mmol) and stirred at  $-78^{\circ}\text{C}$  for 30min. Magnesium bromide etherate (3.6g, 13.9mmol) was added and the
- 15 solution was allowed to warm to  $-45^{\circ}\text{C}$  for 15min. The reaction was cooled to  $-78^{\circ}\text{C}$  and aldehyde 58 (3.26g, 12.7mmol; Graybill et al., Int. J. Protein Res., 44, pp. 173-182 (1993)) in tetrahydrofuran (65mL) was added dropwise. The reaction was stirred for 25min., then
- 20 allowed to warm to  $-40^{\circ}\text{C}$  and stirred for 3h, and then at room temperature for 1h. The reaction was quenched with 5%  $\text{NaHCO}_3$  (12mL) and stirred for 3h. The tetrahydrofuran was removed in vacuo and the resulting residue was extracted with dichloromethane. The
- 25 organic layer was washed with saturated sodium chloride solution and dried over magnesium sulfate, filtered, and concentrated to yield 6.14g of the title compound.

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Purification gave 4.79g (80%) of **99**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.45(s, 9H), 2.7-2.5(m, 2H), 2.8(dd, 1H), 4.2, 4.4(2 x d, 1H), 4.7-4.5(m, 3H), 5.35-5.1(m, 2H), 5.6, 5.7(2 x d, 1H), 6.0-5.8(m, 1H), 7.2(d, 1H), 7.3(m, 1H), 7.4(m, 2H).



**a** R = H

**b** R =  $\text{COCH}_2\text{CH}_2\text{Ph}$

**c** R =  $\text{CH}_2\text{Ph}$

**[2-Oxo-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-yl]acetic acid methyl ester (104a)**. Anhydrous hydrogen chloride was bubbled into a solution of (3(S)-tert-butoxycarbonylamino-2-oxo-2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-yl)acetic acid methyl ester (**103**, 1g, 2.86 mmol) in 25 ml of ethyl acetate for 2 minutes then stirred for 1 hour at room temperature. The reaction was evaporated to give 2-oxo-3(S)-amino-2,3,4,5-

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tetrahydrobenzo[b][1,4]diazepin-1-yl acetic acid methyl ester hydrochloride as a white solid.

The hydrochloride salt and hydrocinnamic acid (0.47 g, 3.15 mmol) were dissolved into 20 ml of

5 dimethylformamide and cooled to 0 °C.

Diisopropylethylamine (1 ml, 5.72 mmol) was added to the solution followed by the addition of N-

hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. After stirring for 18

10 hours at room temperature, the mixture was diluted with 150 ml of ethyl acetate and washed with 10% sodium hydrogen sulfate, 10% sodium bicarbonate, and brine.

The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to a crude solid that

15 was purified by flash chromatography eluting with 7:3 ethyl acetate/dichloromethane to afford 600 mg (55%) of

the title compound as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.3-6.85 (9H, m), 6.55-6.0 (1H, d), 4.88-4.82 (1H, m),

4.72-4.65 (1H, d), 4.28-4.22 (1H, m), 3.95-3.9 (1H, m),

20 3.78 (3H, s), 3.65 (1H, br. s), 3.28-3.2 (1H, m), 2.95-2.84 (2H, m), 2.55-2.4 (2H, m).

**(3(S)-(3-Phenylpropionylamino)-2-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl)acetic acid (105a).**

(3(S)-(3-Phenylpropionylamino)-2-oxo-2,3,4,5-

25 tetrahydro-benzo[b][1,4]diazepin-1-yl)acetic acid methyl ester (**104a**) was dissolved in 90% methanol.

Lithium hydroxide hydrate was added to the reaction and the reaction was stirred at room temperature for 4 h.

The reaction was evaporated in vacuo to give a white

30 solid. This was dissolved in 20 ml of water and acidified to pH 5 and extracted with ethyl acetate to afford 304 mg (88%) of the title compound as a white

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solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.5-6.9 (11H, m), 4.92-4.8 (1H, m), 4.7-4.58 (1H, d), 4.38-4.25 (1H, d), 3.88-3.78 (1H, m), 3.45-3.25 (1H, m), 3.05-2.85 (2H, m), 2.55-2.45 (2H, m).

- 5 4-Oxo-3(S)-(2-[2-oxo-3(S)-(3-phenylpropionylamino)-  
2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-  
ylacetylaminobutyric acid (106a). N-[1-(2-Benzyloxy-  
5-oxotetrahydrofuran-3-ylcarbamoyl-methyl)-2-oxo-  
2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-3-  
10 phenylpropionamide was prepared from 105a by the  
procedure used to prepare compound H (stepA) to afford  
390 mg (93%) of the product as diastereomers.  $^1\text{H}$  NMR  
( $\text{CD}_3\text{OD}$ )  $\delta$  7.58-7.22 (14H, m), 5.78-5.73 (0.5 H, d), 5.64  
(0.5 H, s), 5.0-4.72 (4H, m), 4.54-4.42 (2H, m), 3.82-  
15 3.76 (0.5 H, m), 3.68-3.62 (0.5 H, m), 3.28-3.21 (0.5H,  
m), 3.19-3.12 (0.5H, m), 3.07-2.98 (2H, m), 2.78-2.48  
(4H, m).

- The resulting product was converted to 106a by the  
method described to prepare compound H (StepD) to  
20 afford the title compound as a white solid (17%):  $^1\text{H}$   
NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.54-6.98 (9H, m), 5.58-5.44 (1H, m), 4.8-  
4.2 (4H, m), 3.96-3.3 (2H, m), 3.30-3.05 (1H, m), 2.98-  
2.25 (5H, m).

- [2-Oxo-5-(3-phenylpropionyl)-3(S)-(3-  
25 phenylpropionylamino)-2,3,4,5-  
tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid methyl  
ester (104b). Anhydrous hydrogen chloride was bubbled  
into a solution of (3(S)-tert-butoxycarbonylamino-2-  
oxo-2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-  
30 yl)acetic acid methyl ester (103, 1g, 2.86mmol) in 25

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ml of ethyl acetate for 2 minutes then stirred for 1 hour at room temperature. The reaction was evaporated to give 2-oxo-3(S)-amino-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl acetic acid methyl ester hydrochloride as a white solid.

The hydrochloride salt was suspended into 20 ml of dichloromethane and cooled to 0 °C. Triethylamine (1.6 ml, 11.5 mmol) was added to the suspension followed by the dropwise addition of dihydrocinnamoyl chloride (0.9 ml, 6 mmol). The mixture was warmed to room temperature and stirred for 18 hours. The mixture was diluted with 25 ml of dichloromethane and washed twice with 50 ml of water and once with 50 ml of brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to give a viscous, yellow oil that was purified by flash chromatography eluting with 1:1 ethyl acetate/dichloromethane to afford 1.35 g (92%) of the title product as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.45-7.02 (14 H, m), 6.37-6.32 (1H, d), 4.78-4.72 (1H, m), 4.52-4.3 (3H, m), 3.82-3.77 (1H, m), 3.74 (3H, s), 3.03-2.87 (4H, m), 2.58-2.45 (2H, m), 2.45-2.35 (1H, m), 2.25-2.16 (1H, m).

**[2-Oxo-5-(3-phenylpropionyl)-3-(3(S)-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid (105b).** [2-Oxo-5-(3-phenylpropionyl)-3-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid methyl ester (**104b**; 680 mg, 1.32 mmol) was hydrolyzed by the procedure used to hydrolyze **105a** to afford 645 mg (98%) of the title compound as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.56 (1H, br. s), 7.5-7.42 (1H, m), 7.35-6.95 (14H,

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m), 4.95-4.88 (1H, m), 4.64-4.55 (1H, d), 4.54-4.45 (1H, t), 4.15-4.05 (1H, d), 3.75 (1H, m), 3.05-2.75 (4H, m), 2.58-2.45 (2H, m), 2.45-2.28 (1H, m), 2.25-2.14 (1H, m).

- 5 2-Oxo-3(S)-(2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-phenyl-propionyl-amino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetyl-amino)butyric acid (106b). [2-Oxo-5-(3-phenylpropionyl)-3-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid and 3-amino-4-oxobutyric acid tert-butylester semicarbazone were coupled by the procedure used in the preparation of compound K (step A) to give 350 mg (85%) of a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.05 (1H, br. s), 7.58-7.55 (1H, d), 7.5-7.35 (1H, m), 7.35-6.95 (14 H, m), 6.75-6.72 (1H, d), 6.25 (1H, br. s), 5.25 (1H, br. s), 4.95-4.88 (1H, m), 4.8-4.72 (1H, m), 4.55-4.4 (2H, m), 3.92-3.88 (1H, d), 3.73-3.68 (1H, m), 2.95-2.8 (4H, m), 2.8-2.72 (1H, m), 2.62-2.55 (1H, m), 2.55-2.45 (2H, m), 2.4-2.32 (1H, m), 2.2-2.12 (1H, m), 1.45 (9H, s).
- 15 4-Oxo-3-(2-[2-oxo-5-(3-phenylpropionyl)-3-(3-phenyl-propionyl -amino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-acetyl-amino)butyric acid tert-butyl ester semicarbazone was deprotected as described in the preparation of compound K (step C) to give 118 mg (47%) of the title compound as a white solid. <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.48-6.95 (14 H, m), 4.65-4.15 (6H, m), 3.5-3.4 (1H, m), 2.85-2.72 (4H, m), 2.65-2.5 (1H, m), 2.5-2.34 (3H, m), 2.34-2.15 (2H, m).
- 20 25 30 [5-Benzyl-2-oxo-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-yl]acetic acid

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methyl ester (104c). [2-Oxo-3-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid methyl ester (104a; 500 mg, 1.31 mmol), calcium carbonate (155 mg, 1.58 mmol), and benzyl bromide (170  $\mu$ l, 1.44 mmol) were taken into 10 ml of dimethylformamide and heated to 80 °C for 8 hours. The mixture was diluted with 150 ml of ethyl acetate and washed 4 times with 50 ml of water. The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to give a viscous, yellow oil that was purified by flash chromatography eluting with dichloromethane/ethyl acetate (8:2) to give 460 mg (75%) of the title compound as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.34-7.05 (14 H, m), 6.32-6.28 (1H, d), 4.84-4.76 (1H, d), 4.76-4.70 (1H, m), 4.43-4.37 (1H, d), 4.26-4.18 (1H, d), 4.06-4.00 (1H, d), 3.79 (3H, s), 3.45-3.37 (1H, m), 3.02-2.95 (1H, m), 2.90-2.82 (2H, m), 2.5-2.34 (2H, m).

[5-Benzyl-2-oxo-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-yl]acetic acid (105c) was prepared by the hydrolysis of the ester (102c) by the procedure reported in Example 105a to give 450 mg (98%) of the title compound as a white solid: <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  7.5-7.05 (14 H, m), 6.4 (1H, br. s), 4.85-4.55 (2H, m), 4.5-4.21 (2H, m), 4.12-3.92 (1H, d), 3.45-3.3 (1H, m), 3.1-2.8 (3H, m), 2.55-2.28 (3H, m).

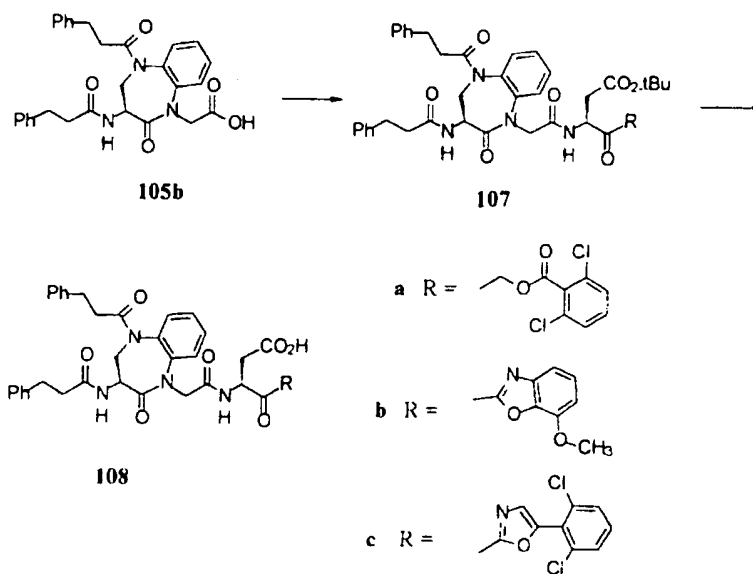
3(S)-(2-[5-Benzyl-2-oxo-3-(3(S)-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-acetylamino)-4-oxobutyric acid (106c). [5-Benzyl-2-



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oxo-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b[1,4]diazepin-1-yl]acetic acid and 3(S)-amino-4-oxobutyric acid tert-butylester semicarbazone were coupled by the procedure used in the preparation of compound **K** (step A) and to afford 260 mg (85%) of a white solid:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.35-7.0 (15 H, m), 4.94-4.88 (1H, m), 4.68-4.58 (1H, d), 4.57-4.52 (1H, m), 4.41-4.34 (1H, d), 4.3-4.23 (1H, d), 4.1-4.04 (1H, d), 3.18-3.11 (1H, m), 3.09-2.98 (1H, m), 2.78-2.72 (2H, t), 2.65-2.57 (1H, m), 2.42-2.33 (3H, m).

3(S)-(2-[5-Benzyl-2-oxo-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b[1,4]diazepin-1-yl]-acetyl-amino]-4-oxobutyric acid tert-butyl ester semicarbazone was deprotected as described in the preparation of compound **K** (step C) to give 168 mg (81%) of the title compound as a white solid.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.37-7.0 (14H, m), 4.75-4.62 (1H, m), 4.6-4.45 (2H, m), 4.4-4.21 (2H, m), 4.15-3.95 (2H, m), 3.15-3.0 (2H, m), 2.82-2.67 (2H, m), 2.65-2.52 (1H, m), 2.5-2.32 (3H, m).



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2,6-Dichlorobenzoic acid 4-tert-butoxycarbonyl-2-oxo-3(S)-(2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetyl-amino)butyl ester

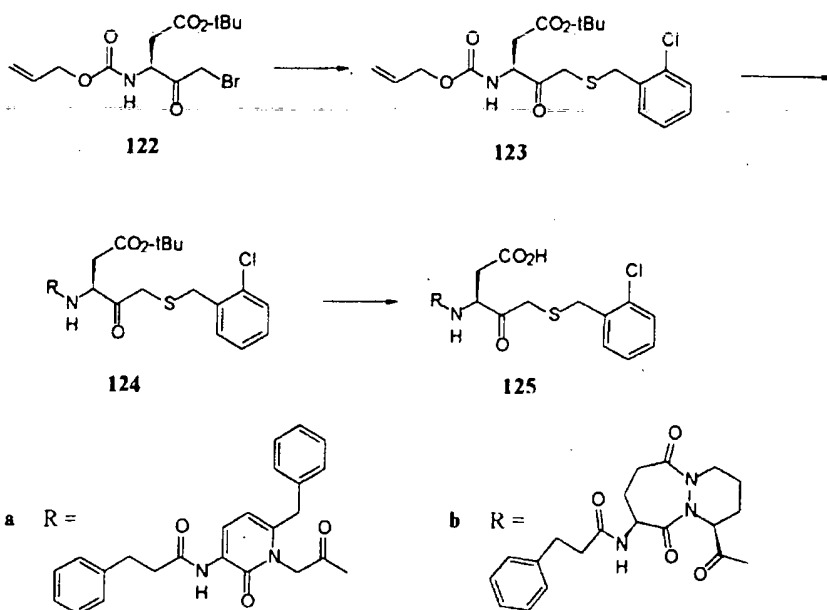
- 5 (107a). The resulting semicarbazone was prepared by the coupling of compound 105b and t-butyl 3-(allyloxycarbonylamino)-4-oxo-5-(2,6-dichlorobenzoyloxy)pentanoate (WO 93 16710) as described in compound 56a to give 256 mg (58%) of the title compound as a
- 10 white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.45-7.04 (17H, m), 6.45-6.34 (2H, m), 5.28-5.21 (1H, m), 5.1-5.0 (1H, m), 4.95-4.90 (1H, m), 4.75-4.70 (1H, m), 4.55-4.44 (1H, m), 4.32-4.22 (1H, dd), 3.99-3.85 (1H, dd), 3.85-3.76 (1H, m), 3.06-2.83 (5H, m), 2.83-2.74 (1H, m), 2.6-2.44 (2H,
- 15 m), 2.43-2.33 (1H, m), 2.24-2.15 (1H, m), 1.45 (9H, s).

- 2,6-Dichlorobenzoic acid 4-carboxy-2-oxo-3(S)-(2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetyl-amino)butyl
- 20 ester (108a) was prepared from 107a by the method described for compound 57a which afforded 156 mg (68%) of the title compound as a white solid. <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.5-6.9 (17H, m), 5.16-5.02 (1H, dd), 4.88-4.71 (2H, m), 4.62-4.44 (2H, m), 4.42-4.28 (2H, m), 4.27-4.18
- 25 (1H, m), 3.47-3.41 (1H, m), 2.90-2.60 (5H, m), 2.46-2.4 (2H, m), 2.39-2.18 (2H, m).

- 4-(7-Methoxybenzoxazol-2-yl)-4-oxo-3(S)-(2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-acetyl-amino)
- 30 butyric acid (108b) was prepared by the method

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described for compound **69a** to give the title compound (50%) as a white solid.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  7.41-6.88 (17H, m), 5.6-5.55 (0.5H, t), 5.48-5.43 (0.5H, t), 4.64-4.45 (2H, m), 4.45-4.30 (1H, m), 3.93 (1.5H, s), 3.90 (1.5H, s), 3.47-3.34 (1H, m), 3.10-2.85 (2H, m), 2.84-2.63 (5H, m), 2.6-2.4 (2H, m), 2.3-2.1 (2H, m).



**t-Butyl (3S) N-(allyloxycarbonyl)-3-amino-5-(2-chlorophenylmethylthio)-4-oxo-pentanoate (123).**

Potassium fluoride (273mg, 4.70mmol) and then 2-chlorophenylmethyl thiol (373mg, 2.35mmol) were added to a stirred solution of (3S) t-butyl N-(allyloxycarbonyl)-3-amino-5-bromo-4-oxo-pentanoate (**122**; 749mg, 2.14mmol; WO 93 16710) in dimethylformamide (20ml). The mixture was stirred for 3.5h, quenched with water (50ml) and extracted with ethyl acetate (2 x 50ml). The combined organic extracts were washed with water (4 x 50ml) then brine

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(50ml). They were dried ( $\text{MgSO}_4$ ) and concentrated to afford an oil which was purified by flash chromatography (10-35% ethyl acetate/hexane) to afford 832 mg (91%) of a colourless solid: mp. 45-6 °C;  $[\alpha]_D^{20}$

5 -19.0° (c 1.0,  $\text{CH}_2\text{Cl}_2$ ); IR (film) 3340, 2980, 2935, 1725, 1712, 1511, 1503, 1474, 1446, 1421, 1393, 1368, 1281, 1244, 1157, 1052, 1040, 995, 764, 739;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.36 (2H, m), 7.21 (2H, m), 5.91 (2H, m), 5.27 (2H, m), 4.76 (1H, m), 4.59 (2H, d), 3.78 (2H, s), 3.36  
10 (2H, m), 2.91 (1H, dd), 2.74 (1H, dd), 1.43 (9H, s).  
Anal. Calcd for  $\text{C}_{20}\text{H}_{26}\text{ClNO}_5\text{S}$ : C, 56.13; H, 6.12; N, 3.27; S, 7.49. Found: C, 56.08; H, 6.11; N, 3.26; S, 7.54. MS (C.I.) 430/28 ( $\text{M}^+ + 1$ , 3%), 374/2 (100).

t-Butyl (3S) 3(2(6-benzyl-1,2-dihydro-2-oxo-3(3-phenylpropionylamino)-1-pyridyl)acetyl-amino-5-(2-chlorophenylmethylthio)-4-oxopentanoate (124a). 6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionylamino)-pyridyl acetic acid (52b; 300mg, 0.76mmol) in THF (7ml) was stirred with 1-hydroxybenzotriazole (205mg,  
20 1.52mmol) and 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride). After 3 min, water (12 drops) was added and the mixture stirred 10min then treated with t-butyl (3S) N-(allyloxycarbonyl)-3-amino-5-(2-chlorophenylmethylthio)-4-oxopentanoate (123)  
25 (325mg, 0.76mmol), bis (triphenylphosphine) palladium II chloride (20mg) and tributyltin hydride (0.6ml, 2.28mmol). The mixture was stirred for 5h at room temperature, poured into ethyl acetate and washed with aqueous 1M HCl (x2), aqueous sodium bicarbonate, brine,  
30 dried ( $\text{MgSO}_4$ ) and concentrated. The residue was triturated with pentane and the supernatant discarded. Chromatography (silica gel, 50% ethyl acetate/hexane)

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afforded a colourless foam (439mg, 81%):  $[\alpha]_D^{22}$  -18.3° (c 0.5, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3356, 3311, 1722, 1689, 1646, 1599, 1567, 1513, 1367, 1154; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.39 (1H, d), 8.23 (1H, s), 7.24 (14H, m), 6.16 (1H, d), 4.95 (1H, m), 4.63 (2H, m), 4.02 (2H, s), 3.74 (2H, s), 3.27 (2H, s), 2.85 (6H, m), 1.40 (9H, s). Anal. Calcd for C<sub>39</sub>H<sub>42</sub>ClN<sub>3</sub>O<sub>6</sub>S: C, 65.39; H, 5.91; N, 5.87. Found: C, 65.51; H, 5.99; N, 5.77.

t-Butyl [3S(1S,9S)]-3-(6,10-dioxo-1,2,3,4,7,8,9,10-octahydro)-9-(3-phenylpropionylamino)-6H-pyridazine[1,2-a][1,2]diazepine-1-carboxamido-5-(2-chlorophenylmethylthio)-4-oxopentanoate (124b) was prepared by a similar method as 124a from the thioether 123 and 3S(1S,9S)-3-(6,10-dioxo-1,2,3,4,7,8,9,10-octahydro)-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid (45a) to afford 452mg (50%) of colourless foam: mp 55-7 °C;  $[\alpha]_D^{22}$  -94.0° (c 0.12, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3288, 2934, 1741, 1722, 1686, 1666, 1644, 1523, 1433, 1260, 1225, 1146, 757; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.35 (3H, m), 7.20 (7H, m), 6.46 (1H, d), 5.21 (1H, m), 4.97 (2H, m), 4.56 (1H, m), 3.75 (2H, s), 3.25 (3H, m), 2.93 (5H, m), 2.71 (1H, dd), 2.55 (2H, m), 2.30 (1H, m), 1.92 (3H, m), 1.66 (2H, m), 1.42 (9H, s). Anal. Calcd for C<sub>35</sub>H<sub>43</sub>ClN<sub>4</sub>O<sub>7</sub>S. 0.25H<sub>2</sub>O: C, 59.73; H, 6.23; Cl, 5.04; N, 7.96; S, 4.56. Found: C, 59.73; H, 6.19; Cl, 5.10; N, 7.79; S, 4.58. MS (-FAB) 697 (M-1, 100).

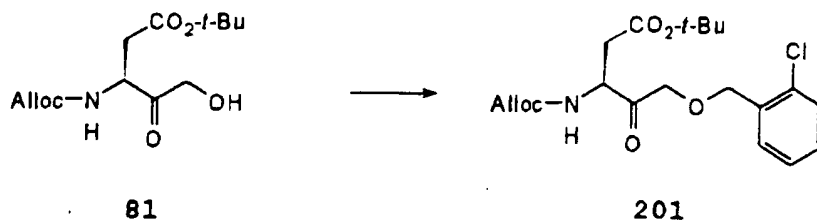
(3S) 3(2(6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionylamino)-1-pyridyl)acetyl-amino-5-(2-chlorophenylmethylthio)-4-oxopentanoic acid (125a).

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t-Butyl-3(2(6-benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionylamino)-1-pyridyl)acetyl-amino-5-(2-chlorophenylmethylthio)-4-oxopentanoate (**124a**) (400mg, 0.56mmol) in dichloromethane (3ml) at 0 °C was treated  
5 with trifluoroacetic acid (3ml) and stirred at 0 °C for 1h and room temperature for 0.5h. The solution was concentrated then redissolved in dichloromethane and reconcentrated. This procedure was repeated three times. The residue was stirred in ether for 1hr and  
10 filtered to yield a colourless solid (364mg, 99%): mp. 165-7 °C;  $[\alpha]_D^{22}$  -27.7 ° (c 0.2, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3289, 1712, 1682, 1657, 1645, 1593, 1562, 1527, 1497, 1416, 1203, 1182; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.47 (1H, d), 8.21 (1H, s), 7.70 (1H, d), 7.22 (14H, m), 6.24 (1H, d), 5.03  
15 (1H, m), 4.65 (2H, m), 4.06 (2H, s), 3.69 (2H, m), 3.23 (2H, m), 2.88 (6H, m).

[3S(1S,9S)]-3-(6,10-dioxo-1,2,3,4,7,8,9,10-octahydro)-9-(3-phenylpropionyl-amino)-6H-pyridazine[1,2-a][1,2]diazepine-1-carboxamido-5-(2-  
20 chlorophenyl-methylthio)-4-oxopentanoic acid (**125b**), was prepared by a similar method as **125a** from the t-butyl ester **124b** to afford 362mg (93%) of colourless powder: mp 76-80 °C;  $[\alpha]_D^{21}$  -134 ° (c 0.10, MeOH); IR (KBr) 3309, 2935, 1725, 1658, 1528, 1445, 1417, 1277,  
25 1219, 1175; <sup>1</sup>H NMR (D<sub>6</sub>-DMSO) δ 8.80 (1H, d), 8.19 (1H, d), 7.31 (9H, m), 5.09 (1H, m), 4.74 (1H, m), 4.63 (1H, m), 4.35 (1H, m), 3.76 (2H, m), 3.28 (3H, m), 2.80 (5H, m), 2.52 (4H, m), 2.16 (2H, m), 1.90 (3H, m). Anal. Calcd for C<sub>31</sub>H<sub>35</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>7</sub>S. 0.25H<sub>2</sub>O: C, 57.49; H, 5.53;  
30 N, 8.65; S, 4.95. Found: C, 57.35; H, 5.43; N, 8.45; S, 4.88. MS (-FAB) 641 (M-1, 100).

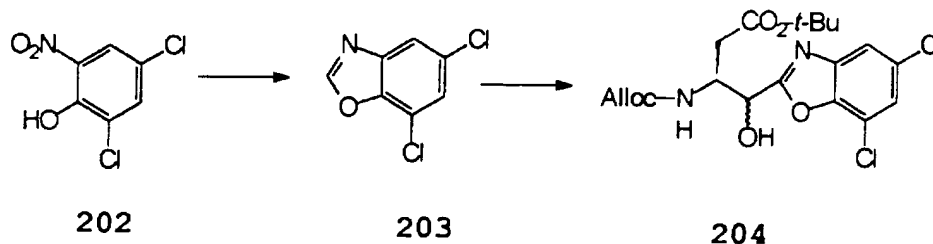
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2-Chlorophenylmethyliodide. A mixture of 2-chlorophenylmethylbromide (4g, 19.47mmol) and NaI (14g, 97.33mmol) in acetone (40ml) was stirred under reflux for 1 hour. The reaction mixture was cooled, filtered and concentrated *in vacuo*. The residue was triturated with hexane and filtered. The solution was concentrated *in vacuo*, and the resulting oil purified by flash chromatography (silica, hexane) to afford the title compound (4.67g, 63%) as an oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.34 (4H, m), 4.54 (2H, s).

(3S) t-Butyl N-(allyloxycarbonyl)-3-amino-5-(2-chlorophenylmethoxy)-4-oxopentanoate (201). (3S) t-Butyl N-(allyloxycarbonyl)-3-amino-5-hydroxy-4-oxopentanoate (81, Chapman, et al., Bioorg. & Med. Chem. Lett., 2, pp. 613-618 (1992) 0.144g, 0.5mmol) and 2-chlorophenylmethyliodide (0.569g, 1.5mmol) in  $\text{CH}_2\text{Cl}_2$  (4ml) were stirred vigorously with silver oxide (0.231g, 1mmol) and heated at 38 °C for 40 hours. The reaction mixture was cooled, filtered and the filtrate evaporated. The residue was purified by flash chromatography (silica, 0-20% ethylacetate in hexane) to afford the product as a colourless oil (0.138g, 67%):  $[\alpha]_D^{24} +3.9^\circ$  (c 1.3,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.37 (4H, m), 5.88 (2H, m), 5.26 (2H, m), 4.69 (2H, s), 4.57 (3H, m), 4.50 (1H, d), 4.35 (1H, d), 3.03 (1H, dd), 2.76 (1H, dd), 1.42 (9H, s).

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**5,7-Dichlorobenzoxazole (203).** A solution of 2,4-dichloro-6-nitrophenol (**202**, 40g containing 20% moisture) in EtOAc (500ml) was dried using  $\text{MgSO}_4$ , filtered and the filter cake washed with a little

5 EtOAc. Platinum on carbon (5% sulphided - 2g) was added and the mixture hydrogenated until uptake of  $\text{H}_2$  ceased. Triethyl orthoformate (160ml) and p-toluene sulphonic acid (160mg) were added and the mixture refluxed for 4h. After cooling and removal of spent

10 catalyst by filtration the solution was washed with sat.  $\text{NaHCO}_3$  solution, water and brine, dried with  $\text{MgSO}_4$  and evaporated to dryness. Trituration with hexane gave a solid which was collected by filtration, washed with hexane and dried to give the title compound

15 (25.5g, 88%) as a crystalline solid: mp 98-99 °C; IR (KBr) 3119, 1610, 1590, 1510, 1452, 1393, 1296, 1067, 850;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.16 (1H, s); 7.69 (1H, d,  $J = 1.9$ ), 7.42 (1H, d,  $J = 1.9$ ); Anal. Calcd for  $\text{C}_7\text{H}_3\text{Cl}_2\text{NO}$ : C, 44.72; H, 1.61; N, 7.45; Cl, 37.70. Found: C,

20 44.84; H, 1.69; N, 7.31; Cl, 37.71.

**(3S,4RS) t-Butyl N-(allyloxycarbonyl)-3-amino-4-hydroxy-4-(5,7-dichlorobenzoxazol-2-yl)butanoate (204).**

Magnesium bromide was prepared by reaction of Mg (7.45g, 0.30mole) in THF (516ml) with  $\text{I}_2$  (50mg) and

25 1,2-dibromoethane (26.3ml, 57.3g, 0.30mole) at reflux for 2h and then cooling to -40 °C. To the above was



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added rapidly via cannula a solution of 2-lithio-5,7-dichlorobenzoxazole at 70 °C (prepared from 5,7-dichlorobenzoxazole (**203**, 28.9g, 0.154mole) and butyl lithium (100ml 1.52M in hexane) in THF (150ml) at -

5 70 °C). The mixture was stirred at -40 °C for 1h and then cooled to -70 °C before adding a solution of (3S) t-butyl N-(allyloxycarbonyl)-3-amino-4-oxo-butanoate (Chapman, et al., Bioorg. & Med. Chem. Lett., 2, pp. 613-618 (1992)) (20.3g, 0.078mole) in THF (160ml) at

10 less than -60 °C. The reaction was allowed to warm to ambient temperature and was stirred for 16h before quenching with ammonium chloride solution and extracting with 1:1 hexane:ethylacetate 600ml. The organic solution was washed with water and brine, dried

15 with MgSO<sub>4</sub> and evaporated to a syrup (52.9g). Flash chromatography (SiO<sub>2</sub> 250g -11 aliquots of 1:1 hexane: CH<sub>2</sub>Cl<sub>2</sub> x2, CH<sub>2</sub>Cl<sub>2</sub>, 5% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>, 10% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>, 20% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>) gave impure product 24.6g which on further chromatography (SiO<sub>2</sub> 1:1 hexane:ether)

20 give the title compound as a golden-brown glass (22.7g, 64%); IR (film) 3343, 2980, 1723, 1712, 1520, 1456, 1398, 1369, 1254, 1158, 993; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.60 (1H, m), 7.37 (1H, m), 5.72 (1H, m), 5.64 (0.5H, d), 5.10 (2.5H, m), 4.7-4.3 (4H, m), 2.9-2.6 (2H, m), 1.46 and

25 1.42 (9H combined, 2 x s). MS ES<sup>+</sup> Da/e 445 (M + 1)<sup>+</sup> C1 35 62%, 447 (M + 1)<sup>+</sup> C1 37 40%, 389 100%.

$$\begin{array}{ccccc}
 t\text{-BuO}_2\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}(\text{NH}_2)-\text{CO}_2\text{H} & \longrightarrow & t\text{-BuO}_2\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}(\text{Alloc-NH})-\text{CO}_2\text{H} & \longrightarrow & t\text{-BuO}_2\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}(\text{Alloc-NH})-\text{CH}_2\text{OH} \\
 & & \text{205a} & & \text{206a} \\
 \text{(a) } * = \text{S} & & & & \\
 \text{(b) } * = \text{R} & & \text{205b} & & \text{206b} \\
 & & & & \downarrow \\
 t\text{-BuO}_2\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}(\text{Alloc-NH})-\text{CH}=\text{N}-\text{N}(\text{H})-\text{C}(=\text{O})\text{NH}_2 & \longleftarrow & t\text{-BuO}_2\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}(\text{Alloc-NH})-\text{CHO} & & \\
 \text{208a} & & \text{207a} & & \\
 \text{208b} & & \text{207b} & & 
 \end{array}$$

(205a). To a mixture of THF (200ml) and water (100ml) containing  $\text{NaHCO}_3$  (16.6g, 0.2mol) was added glutaric acid t-butyl ester (10g, 49.2mmol) and then dropwise over 20 minutes allyl chloroformate (6.8ml, 64mmol). The mixture was stirred for 2 hours, extracted with EtOAc, washed with a sat. hydrogenocarbonate solution, water and a sat. salt solution, dried and evaporated to an oil **205a** (9.5g, 67.2%);  $[\alpha]_D^{20} -6^\circ$  (c 1.5, MeOH)

(205b), was prepared by an analogous method to 205a to afford a colourless oil (6.27g, 88%):  $[\alpha]_D^{20} +16^\circ$  (c 0.095, MeOH); IR (KBr) 3678, 3332, 3088, 2980, 2937, 1724, 1530, 1453, 1393, 1370, 1331, 1255, 1155, 1056, 995, 935, 845, 778, 757, 636, 583;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$

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9.24 (1H, broad s), 5.94-5.79 (1H, m), 5.58 (1H, d),  
5.33-5.17 (2H, m), 4.55 (2H, d), 4.38-4.31 (1H, m),  
2.41-1.95 (4H, m), 1.42 (9H, s); Anal. Calcd for  
 $C_{13}H_{21}NO_6$ : C, 54.35; H, 7.37; N, 4.88. Found: C,  
5 54.4; H, 7.5; N, 4.8.

**(4S) t-Butyl N-allyloxycarbonyl-4-amino-5-**

**hydroxypentanoate (206a).** To a solution of **205a** (3.6g,  
12.5mmol) in THF (100ml) at 0 °C was added N-methyl-  
morpholine (1.5ml, 13mmol) followed by isobutyl  
10 chloroformate, (1.1ml, 13mmol). After 15 minutes, this  
mixture was added to a suspension of  $NaBH_4$  (0.95g,  
25mmol) in THF (100ml) and MeOH (25ml) at -78 °C.  
After 2 hours at -70 °C, the mixture was quenched with  
acetic acid, diluted with EtOAc, washed with a sat.  
15 hydrogenocarbonate solution 3 times, water and a sat.  
solution of salt, dried and evaporated. Flash  
chromatography (2% MeOH in  $CH_2Cl_2$ ) afforded **206a** as a  
colourless oil (2.4g, 70%):  $[\alpha]_D^{20}$  -10 ° (c 3.88,  
 $CH_2Cl_2$ );  $^1H$  NMR ( $CDCl_3$ )  $\delta$  5.84 (1H, m), 5.34-5.17 (3H,  
20 m), 4.56-4.53 (2H, m), 3.68-3.59 (2H, m), 2.98 (1H, m),  
2.40-2.30 (2H, t), 1.84-1.78 (2H, m), 1.43 (9H, s);  
Anal. Calcd for  $C_{13}H_{23}NO_5$ : C, 57.13; H, 8.48; N, 5.12.  
Found: C, 57.1; H, 8.6; N, 6.0

**(4R) t-Butyl N-allyloxycarbonyl-4-amino-5-**

25 **hydroxypentanoate (206b),** was prepared by an analogous  
method to **206a** which afforded the title compound as a  
light yellow oil (3.42g, 57%):  $[\alpha]_D^{20}$  +14 (c 0.166,  
MeOH); IR (KBr) 3341, 3083, 2976, 2936, 2860, 1724,  
1533, 1454, 1419, 1369, 1332, 1251, 1156, 1062, 997,  
30 933, 846, 777, 647;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  5.98-5.81 (1H, m),  
5.35-5.10 (3H, m), 4.55 (2H, d), 3.70-3.56 (3H, m),

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2.50-2.47 (1H, broad s), 2.37-2.30 (2H, m), 1.89-1.74 (2H, m), 1.44 (9H, s); Anal. Calcd for  $C_{13}H_{23}NO_5$ : C, 57.13; H, 8.48; N, 5.12. Found: C, 56.9; H, 8.6; N, 5.6

- 5   **(4S) t-Butyl N-Allyloxycarbonyl-4-amino-5-oxopentanoate (207a)**. To a solution of DMSO (1.51g, 19.3mmol) in  $CH_2Cl_2$  (25ml) at  $-70^\circ C$  was added oxalyl chloride (1.34g, 19.3mmol). After 10 minutes at  $-70^\circ C$ , a solution of (206a) (2.4g, 8.8mmol) in  $CH_2Cl_2$  (10ml) was  
10 added dropwise and the mixture stirred for 15 minutes at  $-70^\circ C$ . Diisopropylethylamine (3.4g, 26.3mmol) was added and the mixture stirred at  $-25^\circ C$  for 15 minutes then diluting with EtOAc (50ml) washed with a solution of sodium hydrogen sulfate 2M, concentrated to give an  
15 oil which was used immediately without purification:  
 $^1H$  NMR ( $CDCl_3$ )  $\delta$  9.5 (1H, s), 6.0-5.5 (2H, m), 5.5-5.1 (2H, m), 4.5 (2H, m), 4.2 (1H, m), 2.4-2.10 (2H, m), 2.05 (2H, m), 1.36 (9H, s).

- (4R) t-Butyl N-Allyloxycarbonyl-4-amino-5-oxopentanoate (207b)**, was prepared by an analogous method to 207a  
20 which afforded an oil (2.95g, 96%) which was used without further purification in the next step:  $[\alpha]_D^{20} +21^\circ$  (c 0.942, MeOH);  $^1H$  NMR ( $CDCl_3$ )  $\delta$  9.58 (1H, s), 6.05-5.80 (1H, m), 5.57 (1H, broad s), 5.35-5.18 (2H, m), 4.56 (2H, d), 4.34-4.24 (1H, m), 2.38-2.16 (3H, m),  
25 1.96-1.73 (1H, m), 1.43 (9H, s).

- (4S) t-Butyl N-Allyloxycarbonyl-4-amino-5-oxopentanoate semicarbazone (208a)**. To a solution of 207a (2.39g, 8.8mmol), in MeOH (20ml) was added sodium acetate  
30 (0.72g, 8.8mmol) and semicarbazide (0.98g, 8.8mmol)

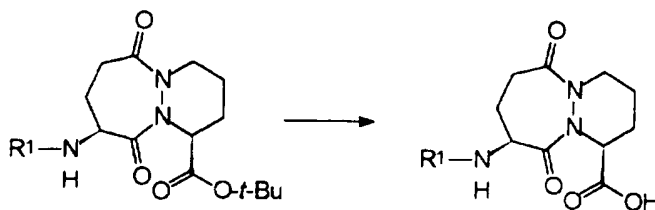
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stirred overnight, concentrated and diluted with  $\text{CH}_2\text{Cl}_2$  (100ml), washed with water, dried and concentrated.

Flash chromatography (2% MeOH in  $\text{CH}_2\text{Cl}_2$ ) afforded **208a** (2.10g, 73%) as an oil:  $[\alpha]_D^{20} -21$  (c 2.55°,  $\text{CH}_2\text{Cl}_2$ );

5  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  9.98 (1H, s), 7.27 (1H, d), 5.8 (1H, m), 5.5 (1H, d), 5.35-5.19 (2H, m), 4.58 (2H, m), 4.14 (1H, m), 2.37 (2H, t), 2.09 (1H, m), 2.0-1.75 (2H, m);  
Anal. Calcd for  $\text{C}_{14}\text{H}_{24}\text{N}_4\text{O}_5$ : C, 51.21; H, 7.37; N, 17.06. Found: C, 50.2; H, 7.3; N, 16.1

10 **(4R) t-Butyl N-Allyloxycarbonyl-4-amino-5-oxopentanoate semicarbazone (208b)**, was prepared by an analogous method to **208a** which afforded a glassy oil (2.37g, 66%):  $[\alpha]_D^{20} +30$  (c 0.26,  $\text{CHCl}_3$ ); IR (KBr) 3476, 3360, 2979, 2923, 1700, 1586, 1527, 1427, 1394, 1369, 1338,  
15 1253, 1156, 1060, 997, 929, 846, 775;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  9.87 (1H, s), 7.09 (1H, d), 6.05-5.75 (3H, m), 5.58 (1H, d), 5.32-5.16 (2H, m), 4.54 (2H, d), 4.35 (1H, m), 2.32-2.26 (2H, m), 2.15-1.55 (2H, m), 1.41 (9H, s);  
Anal. Calcd for  $\text{C}_{14}\text{H}_{24}\text{N}_4\text{O}_5$ : C, 51.21; H, 7.37; N, 17.06. Found: C, 51.0; H, 7.5; N, 16.7.



211 (b)  $\text{R}^1 = \text{MeSO}_2$   
(c)  $\text{R}^1 = \text{MeCO}$   
(d)  $\text{R}^1 = \text{PhCH}_2\text{OCO}$   
(e)  $\text{R}^1 = \text{PhCO}$   
25 (f)  $\text{R}^1 = \text{Fmoc}$

212 (b)  $\text{R}^1 = \text{MeSO}_2$   
(c)  $\text{R}^1 = \text{MeCO}$   
(d)  $\text{R}^1 = \text{PhCH}_2\text{OCO}$   
(e)  $\text{R}^1 = \text{PhCO}$   
(f)  $\text{R}^1 = \text{Fmoc}$

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- (1S,9S) t-Butyl 6,10-dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxylate (**211b**). A solution of t-butyl 9-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (GB 2,128,984; 831mg, 2.79mmol) and diisopropylethylamine (1.22ml, 6.99mmol, 2.5 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (10ml) under dry nitrogen was treated with methanesulphonyl chloride (237μl, 3.07mmol 1.1 equiv). The mixture was stirred for 1h, diluted with EtOAc (75ml) and washed with saturated NaHCO<sub>3</sub> (50ml) and saturated aqueous sodium chloride (30ml), dried (MgSO<sub>4</sub>) and concentrated. Flash chromatography (10-35% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>) afforded **211b** (806mg, 77%) as a colourless solid: mp 68-70 °C;  $[\alpha]_D^{23}$  -109 (c 1.09, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3270, 2980, 2939, 1735, 1677, 1458, 1447, 1418, 1396, 1370, 1328, 1272, 1252, 1232, 1222, 1156, 1131, 991; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 6.15 (1H, d), 5.31 (1H, m), 4.65-4.11 (2H, m), 3.47 (1H, m) 2.99 (3H, s), 2.89 (1H, m), 2.72-2.51 (2H, m), 2.34 (1H, m), 2.26 (1H, m), 2.05-1.62 (4H, m), 1.47 (9H, s); Anal. Calcd for C<sub>15</sub>H<sub>23</sub>N<sub>3</sub>O<sub>6</sub>S: C, 47.97; H, 6.71; N, 11.19; S, 8.54. Found: C, 48.28; H, 6.68; N, 10.86; S, 8.28. MS (+FAB) 376 (M<sup>+</sup> + 1, 66%), 320 (100).
- (1S,9S) t-Butyl 9-acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino [1,2-a]-[1,2]diazepine-1-carboxylate (**211c**). Acetic anhydride (307mg, 3.01mmol) was added to a stirred mixture of t-butyl 9-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (GB 2,128,984; 813.7mg, 2.74mmol), diisopropylethylamine (884mg, 6.84mmol) and CH<sub>2</sub>Cl<sub>2</sub>

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(20ml). The mixture was kept for 1h then diluted with EtOAc, washed with NaHCO<sub>3</sub> solution then brine, dried (MgSO<sub>4</sub>) and concentrated to yield a colourless oil. The product was purified by flash chromatography (0.5-  
5 8% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to afford **211c** (804mg, 71%) of colourless powder: mp 162-3 °C;  $[\alpha]_D^{23}$  -109 (c 1.03, CH<sub>2</sub>Cl<sub>2</sub>); IR(KBr) 3358, 2974, 1733, 1693, 1668, 1528, 1462, 1431, 1406, 1371, 1278, 1271, 1250, 1233, 1217, 1154, 1124;  $\delta$  <sup>1</sup>H NMR (CDCl<sub>3</sub>) d 6.32 (1H, d), 5.29-5.25  
10 (1H, m), 4.98-4.85 (1H, m), 4.68-4.58 (1H, m), 3.55-3.39 (1H, m), 2.91-2.66 (2H, m), 2.39-2.18 (2H, m), 2.03 (3H, s), 1.88-1.64 (4H, m), 1.47 (9H, s); Anal. Calcd for C<sub>16</sub>H<sub>25</sub>N<sub>3</sub>O<sub>5</sub>: C, 56.62; H, 7.43; N, 12.38. Found: C, 56.62; H, 7.43; N, 12.36; MS (+ FAB) 340 (M<sup>+</sup>  
15 + 1, 40%), 284 (100).

(1S,9S) t-Butyl 9-(benzyloxycarbonylamino)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (**211d**). Benzyl chloroformate (1.07g) was added dropwise to a stirred ice cold  
20 mixture of the (1S,9S) t-butyl 9-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (GB 2,128,984; 1.55g, 5.21mmol), NaHCO<sub>3</sub> (0.66g, 7.82mmol), dioxan (32ml) and water (8ml). The mixture was kept at 5 °C for 15min  
25 then for 2h at room temperature. The mixture was diluted with EtOAc (50ml), washed twice with sat. NaHCO<sub>3</sub> solution, dried (MgSO<sub>4</sub>) and concentrated. The oily residue was purified by flash chromatography to afford **211d** (1.98g, 88%) of a colourless oil:  $[\alpha]_D^{24}$  -  
30 56.4 (c 1.0, CH<sub>2</sub>Cl<sub>2</sub>); IR(thin film) 3325, 2979, 2946, 1728, 1677, 1528, 1456, 1422, 1370, 1340, 1272, 1245, 1156, 1122, 1056, 916, 734, 699; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.29

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(5H, m), 5.81-5.72 (1H, m), 5.26-5.20 (1H, m), 5.05 (2H, s), 4.69-4.51 (2H, m), 3.48-3.36 (1H, m), 2.81-2.51 (2H, m), 2.34-2.19 (2H, m), 1.90-1.54 (4H, m), 1.41 (9H, s); Anal. Calcd for  $C_{22}H_{29}N_3O_6 \cdot H_2O$ : C, 58.79; H, 6.92; N, 9.35. Found: C, 59.10; H, 6.57; N, 9.25; MS (ES +) 454 ( $M^+ + Na$ , 87%), 432 ( $M^+ + 1$ , 100).

(1S,9S) t-Butyl 9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxylate (**211e**). A solution of benzoyl chloride (1.61g, 11.47mmol) in  $CH_2Cl_2$  (15ml) was added dropwise to a stirred ice cold mixture of (1S,9S) t-butyl 9-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (GB 2,128,984; 3.1g, 10.43mmol), dry  $CH_2Cl_2$  (20ml) and diisopropylethylamine (4.54ml, 26.06mmol). The mixture was kept cold for 1h then left at room temperature for 0.5h. The mixture was diluted with  $CH_2Cl_2$ , washed twice with brine, dried ( $MgSO_4$ ) and concentrated. The residue was purified by flash chromatography (0-5% metha: 1 in  $CH_2Cl_2$ ) to afford **211e** (4.0g, 96%) of a colourless glass: mp 74-76 °C;  $[\alpha]_D^{30}$  -75.0 ° (c 0.12,  $CH_2Cl_2$ ). IR (KBr) 3350, 2979, 2938, 1736, 1677, 1662, 1536, 1422, 1276, 1250, 1155;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  8.72 (2H, m), 7.53-7.40 (3H, m), 7.07 (1H, d,  $J = 7.2$ ), 5.30 (1H, dd,  $J = 3.0, 5.8$ ), 5.12 (1H, m), 4.66 (1H, m), 3.51 (1H, m), 2.90 (2H, m), 2.38 (1H, dd,  $J 13.2, 6.8$ ), 2.25 (1H, m), 1.9 (2H, m), 1.70 (1H, m). Anal. Calcd for  $C_{21}H_{27}N_3O_5 \cdot 0.5H_2O$ : C, 61.45; H, 6.88; N, 10.24. Found C, 61.69; H, 6.71; N, 10.18.

(1S,9S) t-Butyl 6,10-dioxo-9-(fluoren-9-ylmethoxy-carbonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-



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pyridazino[1,2-a][1,2]-diazepine-1-carboxylate (211f), was prepared in a similar manner to 211e, except 9-fluorenylmethylchloroformate was used instead of benzoylchloride to give a white glassy solid 211f

- 5 (2.14g, 89%): mp 190-192 °C;  $[\alpha]_D^{25}$  -81.5 ° (c 0.1, CH<sub>2</sub>Cl<sub>2</sub>). IR (KBr) 3335, 2977, 1731, 1678, 1450, 1421, 1246, 1156, 742; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.60 (2H, m), 7.57 (2H, m), 7.50-7.26 (4H, m), 5.60 (1H, d, J = 7.8), 5.28 (1H, m), 4.67 (2H, m), 4.38 (2H, m), 4.23 (1H, m),  
10 3.59-3.41 (1H, m), 2.92-2.65 (2H, m), 2.41-2.21 (2H, m), 1.95-1.58 (4H, m), 1.47 (9H, s). MS(ES<sup>-</sup>, m/z) 520 (M<sup>+</sup> + 1, 97%), 179 (100%).

(1S,9S) 6,10-Dioxo-9-methsulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-

- 15 [1,2-a][1,2]diazepine-1-carboxylic acid (212b), was synthesized by the same method as compound 212e (635mg, 85%) as a colourless powder: mp 209-12 °C;  $[\alpha]_D^{24}$  -132 (c 0.12, MeOH); IR (KBr) 3308, 2940, 1717, 1707, 1699, 1619, 1469, 1456, 1442, 1417, 1391, 1348, 1339, 1330,  
20 1310, 1271, 1247, 1222, 1175, 1152, 1133, 993, 976; <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 5.35 (1H, m), 4.58-4.48 (1H, m), 4.46-4.36 (1H, m), 3.60-3.42 (1H, m), 3.01-2.87 (1H, m), 2.95 (3H, s), 2.55-2.39 (1H, m), 2.32-2.20 (2H, m), 2.09-1.89 (2H, m), 1.78-1.62 (2H, m); Anal. Calcd for  
25 C<sub>11</sub>H<sub>17</sub>N<sub>3</sub>O<sub>6</sub>S: C, 41.37; H, 5.37; N, 13.16; S, 10.04. Found: C, 41.59; H, 5.32; N, 12.75; S, 9.76; MS(ES<sup>-</sup>). Accurate Mass calculated for C<sub>11</sub>H<sub>18</sub>N<sub>3</sub>O<sub>6</sub>S (MH<sup>+</sup>): 320.0916. Found: 320.0943.

- (1S,9S) 9-Acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-  
30 octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid (212c), was prepared from 211e the same

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method as compound **212e** as a white glassy solid (595mg, 77%): mp >250 °C;  $[\alpha]_D^{24}$  -153 (c 0.10, MeOH); IR (KBr) 3280, 2942, 1742, 1697, 1675, 1650, 1616, 1548, 1470, 1443, 1281, 1249, 1202, 1187, 1171;  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  5.35-5.31 (1H, m), 4.81-4.71 (1H, m), 4.61-4.46 (1H, m), 3.59-3.44 (2H, m), 3.11-2.94 (1H, m), 2.58-2.39 (1H, m), 2.36-2.19 (2H, m), 2.11-1.83 (3H, m), 1.99 (3H, s), 1.78-1.56 (2H, m); Anal. Calcd for  $\text{C}_{12}\text{H}_{17}\text{N}_3\text{O}_5$ : C, 50.88; H, 6.05; N, 14.83. Found: C, 50.82; H, 6.02; N, 14.58; MS (ES -) 282 (M-1, 100%): Accurate Mass calculated for  $\text{C}_{12}\text{H}_{18}\text{N}_3\text{O}_5$  ( $\text{MH}^+$ ): 284.1246. Found: 284.1258.

**(1S,9S) 9-Benzoyloxycarbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxylic acid (212d)**, was prepared from **211d** by the same method as compound **212e** as colourless crystals (170mg, 97%): mp 60-100 °C;  $[\alpha]_D^{22}$  -103 (c 0.10, MeOH); IR (KBr) 3341, 2947, 1728, 1675, 1531, 1456, 1422, 1339, 1272, 1248, 1221, 1174, 1122, 1056, 982, 699;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.35 (5H, s), 5.65 (1H, d), 5.48-5.40 (1H, m), 5.10 (2H, s), 4.76-4.57 (2H, m), 3.49-3.30 (2H, m), 2.92-2.59 (2H, m), 2.40-2.27 (2H, m), 1.97-1.67 (4H, m); MS (ES -) 374 (M - 1, 100%). Accurate mass calculated for  $\text{C}_{18}\text{H}_{22}\text{N}_3\text{C}_6$  ( $\text{MH}^+$ ): 376.1509. Found: 376.1483. Accurate mass calculated for  $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_6\text{Na}$  ( $\text{MNa}^+$ ): 398.1328. Found: 398.1315.

**(1S,9S) 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxylic acid (212e)**. TFA (20ml) was added to an ice cold stirred solution of the t-butyl ester **211e** (4.15g,

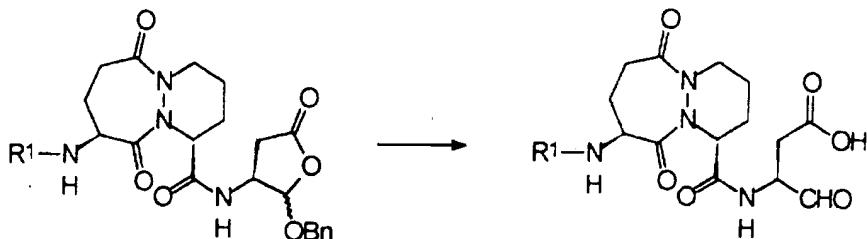
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10.34mmol) in dry  $\text{CH}_2\text{Cl}_2$  (20ml). The mixture was kept cold for 1.5h then left for 2.5h at rt, concentrated. TFA was removed by repeated concentrations of  $\text{CH}_2\text{Cl}_2$ /ether and ether solutions of the residue.

- 5 Finally trituration of the residue with ether afforded **212e** 3.05g (85%) of a white glassy solid: mp 118-126 °C;  $[\alpha]_D^{24}$  -70.5 ° (c 0.1,  $\text{CH}_2\text{Cl}_2$ ). IR (KBr) 3361, 2943, 1737, 1659, 1537, 1426, 1220, 1174;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.80 (2H, m), 7.54-7.33 (4H, m), 8.83 (brs),  
10 5.44 (1H, m), 5.26-5.13 (1H, m), 4.66 (1H, m), 3.59-3.41 (1H, m), 2.97, 2.76 (2H, 2m), 2.36 (2H, m), 1.98 (2H, m), 1.75 (2H, m). MS( $\text{ES}^-$ , m/z) 344 ( $\text{M}^-$  - 1, 100%).

- (1*S*,9*S*) 6,10-Dioxo-9(fluoren-9-ylmethyloxycarbonylamino)-1,2,3,4,7,8,9,10-octahydro-  
15 6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxylic acid (**212f**), was prepared from **211f** in 96% yield by the same method as for **212e**: mp 120-126 °C;  $[\alpha]_D^{25}$  -72.5 ° (c 0.1,  $\text{CH}_2\text{Cl}_2$ ). IR (KBr) 3406, 2950, 1725, 1670, 1526, 1449, 1421, 1272, 1248, 1223, 1175, 761, 741;  
20  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.76 (2H, m), 7.62-7.26 (4H, m), 6.07, 5.76 (2H, brs, d, d,  $J$  = 2.9), 5.46, 5.36 (1H, 2m), 4.79-4.54 (2H, m), 4.77 (2H, m), 4.21 (1H, m), 3.41 (1H, m), 2.89 (1H, m), 2.69 (1H, m), 2.35 (2H, m), 1.98, 1.73 (4H, 2m). MS( $\text{ES}^-$ , m/z) 462 ( $\text{M}^-$  - 1, 50%),  
25 240 (100%).

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(213) (c)  $R^1 = \text{MeCO}$   
 (e)  $R^1 = \text{PhCO}$

(214) (c)  $R^1 = \text{MeCO}$   
 (e)  $R^1 = \text{PhCO}$

[2*RS*, 3*S*(1*S*, 9*S*)] N-(2-Benzoyloxy-5-oxotetrahydrofuran-3-yl)-9-(acetylamino)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide (213c), was synthesized from 212c by the same method as compound 213e to afford a mixture of diastereomers (193mg, 36%) as colourless crystals: IR (KBr) 3272, 1799, 1701, 1682, 1650, 1555, 1424, 1412, 1278, 1258, 1221, 1122, 937;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.41-7.28 (5H, m), 6.52 (0.5H, d), 6.38 (0.5H, d), 6.22 (0.5H, d), 5.57 (0.5H, d), 5.36 (0.5H, s) 5.10-5.05 (1H, m), 5.00-4.45 (5.5H, m), 3.19-2.84 (3H, m), 2.72-2.56 (1H, m), 2.51-2.25 (2H, m), 2.02 (3H, s), 1.98-1.70 (3H, m), 1.66-1.56 (3H, m); Anal. Calcd for  $\text{C}_{23}\text{H}_{28}\text{N}_4\text{O}_7$ : C, 58.47; H, 5.97; N, 11.86. Found: C, 58.37; H, 6.09; N, 11.47. MS (ES<sup>-</sup>) 471 (M-1, 100%). Accurate mass calculated for  $\text{C}_{23}\text{H}_{29}\text{N}_4\text{O}_7$  ( $\text{MH}^+$ ): 473.2036. Found: 473.2012. Accurate mass calculated for  $\text{C}_{23}\text{H}_{28}\text{N}_4\text{O}_7\text{Na}$  ( $\text{MNa}^+$ ): 495.1856. Found: 495.1853.

[1*S*, 9*S*(2*RS*, 3*S*)] 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6*H*-pyridazino[1,2-*a*][1,2]-diazepine-1-carboxamide (213e). Tributyltin hydride (2.2ml, 8.18mmol) was added dropwise to a solution of

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acid **212e** (1.95g, 5.6mmol), (3*S*, 2*RS*) 3-allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydrofuran (Chapman, Bioorg. & Med. Chem. Lett., 2, pp. 615-618 (1992); 1.80g, 6.16mmol) and (Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub> (50mg) in dry CH<sub>2</sub>Cl<sub>2</sub> (36ml), with stirring, under dry nitrogen. After 5 min 1-hydroxybenzotriazole (1.51g, 11.2mmol 6.72mmol) was added followed after cooling (ice/H<sub>2</sub>O) by ethyldimethylaminopropyl carbodiimide hydrochloride (1.29g, 6.72mmol). After 5 mins the cooling bath was removed and the mixture was kept at room temperature for 4h, diluted with EtOAc, washed with 1M HCl, brine, sat. aq. NaHCO<sub>3</sub> and brine, dried (MgSO<sub>4</sub>) and concentrated. Flash chromatography (silica gel, 0-90% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>) gave the product as a white solid (2.34g, 78%): IR (KBr) 3499, 1792, 1658, 1536, 1421, 1279, 1257, 1123, 977, 699; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.81 (2H, m), 7.54-7.34 (8H, m), 7.1, 6.97, 6.89, 6.48 (2H, m, d, *J* 7.7, d, *J* = 7.5, d, *J* = 7.6), 5.57, 5.28 (1H, d, *J* = 5.2, s), 5.23-5.07 (2H, m), 4.93-4.42, 3.22-2.70, 2.51-2.26, 2.08-1.69, 1.22 (15H, 5m). Anal. Calcd for C<sub>28</sub>H<sub>30</sub>N<sub>4</sub>O<sub>7</sub> 0.5H<sub>2</sub>O: C, 61.87; H, 5.75; N, 10.32. Found C, 62.02; H, 5.65; N, 10.25.

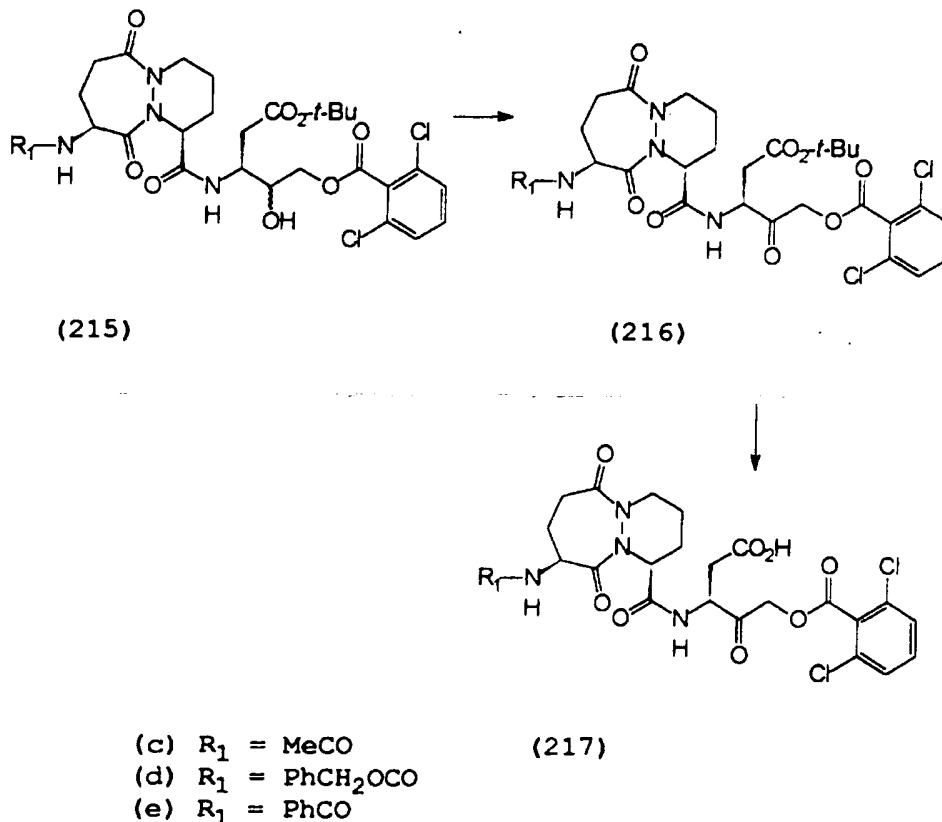
[3*S*(1*S*,9*S*)] 3-(9-Acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-*a*][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (**214c**), was synthesized from **213c** by a method similar to the method used to synthesize **214e** from **213e** to provide colourless crystals (140mg, 99%): mp 90-180 °C; [α]<sub>D</sub><sup>22</sup> -114 (c 0.10, MeOH); IR (KBr) 3334, 3070, 2946, 1787, 1658, 1543, 1422, 1277, 1258; <sup>1</sup>H NMR (d<sup>6</sup>-DMSO) δ 8.66 (1H, m), 8.18 (1H, d), 6.76 (1H, s), 5.08 (1H, m), 4.68 (1H, m), 4.30 (1H, m), 2.92-2.70 (2H, m),

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2.27-2.06 (3H, m), 1.95-1.72 (4H, m), 1.85 (3H, s), 1.58 (2H, m); MS(ES -) 381 (M-1, 100%); Accurate mass calculated for  $C_{16}H_{23}N_4O_7$  ( $MH^+$ ): 383.1567. Found: 383.1548.

- 5 [3S(1S,9S)] 3-(9-Benzoylamino-6,10-dioxo-  
1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-  
diazepine-1-carboxamido)-4-oxobutanoic acid (214e). A  
mixture of 213e (2.29g, 4.28mmol), 10% palladium on  
carbon (1.8g) and MeOH (160ml) was stirred under  $H_2$  at  
10 atmospheric pressure for 6.3h. After filtering and  
concentrating the hydrogenation was repeated with fresh  
catalyst (1.8g) for 5h. After filtering and  
concentrating the residue was triturated with diethyl  
ether, filtered and washed well with ether to give 214e  
15 as a white solid (1.67g, 88%): mp 143-147 °C;  $[\alpha]_D^{23}$  -  
125 ° (c 0.2,  $CH_3OH$ ). IR (KBr) 3391, 1657, 1651, 1538,  
1421, 1280, 1258;  $^1H$  NMR ( $CD_3OD$ )  $\delta$  7.90 (2H, m), 7.63-  
7.46 (3H, m), 5.25 (1H, m), 5.08-4.85 (1H, m), 4.68-  
4.53 (2H, m), 4.33-4.24 (1H, m), 3.62-3.44, 3.22-3.11,  
20 2.75-2.21, 2.15-1.92, 1.73-1.66 (11H, 5m). Anal. Calcd  
for  $C_{21}H_{24}N_4O_7 \cdot H_2O$ : C, 54.54; H, 5.67; N, 12.11. Found  
C, 54.48; H, 5.63; N, 11.92.

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- 5 [3*S*,4*RS*(1*S*,9*S*)] *t*-Butyl 3-[9-acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino-[1,2-*a*][1,2]diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-hydroxypentanoate (215*c*), was synthesized from 214*c* by the same method as compound
- 10 215*e*, to afford a mixture of diastereomers as a white glassy solid (398mg, 84%): IR (KBr) 3338, 2977, 1738, 1658, 1562, 1541, 1433, 1368, 1277, 1150;  $^1\text{H}$  NMR (CDCl<sub>3</sub>)  $\delta$  7.36-7.32 (3H, m), 6.91 (1H, d), 6.30 (1H, d), 5.15-5.09 (1H, m) 5.01-4.88 (1H, m), 4.61-4.44 (2H, m), 4.37-4.08 (3H, m), 3.32-3.18 (1H, m), 3.04-2.89 (1H, m), 2.82-2.51 (4H, m), 2.39-2.29 (1H, m), 2.08-1.64 (4H, m) 2.02 (3H, s); Anal. Calcd for
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$C_{28}H_{34}N_4Cl_2O_9$ : C, 52.26; H, 5.64; N, 8.71. Found: C, 52.44; H, 5.87; N, 8.16. MS (ES -) 645/3/1 (M-1, 26%), 189 (81), 134 (100). Accurate mass calculated for  $C_{28}H_{37}N_4Cl_2O_9$  (MH<sup>+</sup>): 643.1938. Found: 643.1924.  
5 Accurate mass calculated for  $C_{28}H_{36}N_4Cl_2O_9Na$  (MNa<sup>+</sup>) 665.1757. Found: 665.1756.

[3S,4RS(1S,9S)] t-Butyl 3-(9-benzyloxycarbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-5-(2,6-  
10 dichlorobenzyloxy)-4-hydroxypentanoate (215d), was synthesized from 214d by the same method as compound 215e to afford a mixture of diastereomers (657mg, 70%) as a glassy white solid: IR (KBr) 3420, 3361, 2975, 2931, 1716, 1658, 1529, 1434, 1367, 1348, 1250, 1157,  
15 1083, 1055; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.32 (8H, m), 7.14 (1H, d), 5.81 (1H, d), 5.15 (1H, m), 5.07 (2H, s), 4.74-4.65 (1H, m), 4.58-4.22 (4H, m), 4.15-4.06 (1H, m), 3.72 (1H, m), 3.32-3.21 (1H, m), 3.04-2.94 (1H, m), 2.69-2.52 (3H, m), 2.33-2.27 (1H, m), 1.95-1.59 (4H, m),  
20 1.28 (9H, s); Anal. Calcd for  $C_{34}H_{40}N_4Cl_2O_{10} \cdot 0.5 H_2O$ : C, 54.70; H, 5.54; N, 7.50. Found: C, 54.98; H, 5.59; N, 7.24. MS (ES -) 737/5/3 (M-1, 22%), 193/1/89 (100). Accurate mass calculated for  $C_{34}H_{41}N_4Cl_2O_{10}$  (MH<sup>+</sup>) 735.2120. Found: 735.2181.

25 [3S,4RS(1S,9S)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-5-(2,6-dichlorobenzyloxy)-4-hydroxypentanoate (215e),  
Tributyltin hydride (4.6ml; 11.4mmol) was added  
30 dropwise to a stirred mixture of (3S,4RS) t-Butyl (N-allyloxycarbonyl)-3-amino-5-(2,6-dichlorobenzoyloxy)-4-



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hydroxypentanoate (prepared by a method similar to the method described in Revesz et al., Tetrahedron. Lett., 35, pp. 9693-9696 (1994)) (2.64g; 5.7mmol), (Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub> (50mg), CH<sub>2</sub>Cl<sub>2</sub> (100ml) and DMF (20ml) at room temperature. The mixture was stirred for a further 10min was then 1-hydroxybenzotriazole (1.54g, 11.4mmol) was added. The mixture was cooled to 0 °C then ethyldimethylaminopropyl carbodiimide hydrochloride (1.31g; 6.84mmol) added. The mixture was kept at this temperature for 15min then at room temperature for 17h. The mixture was diluted with EtOAc (300ml), washed with 1M HCl (2x100ml), sat. aq. NaHCO<sub>3</sub> (3x100ml) and brine (2x100ml), dried (MgSO<sub>4</sub>) and concentrated. The residue was purified by flash chromatography (2-5% (MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to afford 3.24g (81%) of **215e** as a glassy solid: mp 106-110 °C; IR (KBr) 3354, 1737, 1659, 1531, 1433, 1276, 1150; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.80 (2H, dd, J = 7.9 and 1.5), 7.75-7.26 (6H, m), 7.14-6.76 (2H, m), 5.30-5.02 (2H, m), 4.63-4.11 (5H, m), 3.44-3.26 (2H, m), 3.10-2.30 (5H, m), 2.10-1.60 (5H, m), 1.44 (9H, s); Anal. Calcd for C<sub>33</sub>H<sub>38</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>9</sub> · 0.75H<sub>2</sub>O: C, 55.12; H, 5.54; N, 7.79; Cl, 9.86. Found: C, 55.04; H, 5.34; N, 7.80; Cl, 10.24. MS (ES +) 709/7/5 (M + 1), 378 (59), 324 (64), 322 (100).

[3*S*(1*S*,9*S*)] t-Butyl 3-(9-acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-oxopentanoate (**216c**), was synthesized from **215c** by the same method as compound **216e** as a glassy white solid (300mg, 83%): mp 80-125 °C; [α]<sub>D</sub><sup>23</sup> -89.1 (c 1.08, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3356, 2979, 2935, 1740, 1659, 1532,

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1434, 1369, 1276, 1260, 1151;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.39-7.32 (3H, m), 7.13 (1H, d), 6.34 (1H, d), 5.22-5.17 (1H, m), 5.11 (1H, d), 5.04 (1H, d), 4.99-4.88 (2H, m), 4.64-4.52 (1H, m), 3.29-3.11 (1H, m), 3.05-2.67 (4H, m), 2.39-2.29 (1H, m), 2.02 (3H, s), 1.98-1.75 (4H, m), 1.46 (9H, s); Anal. Calcd for  $\text{C}_{28}\text{H}_{34}\text{N}_4\text{Cl}_2\text{O}_9$ : C, 52.42; H, 5.34; N, 8.73. Found: C, 52.53; H, 5.70; N, 7.85. MS (ES  $-$ ) 643/41/39 (M-1, 100%). Accurate mass calculated for  $\text{C}_{28}\text{H}_{35}\text{N}_4\text{Cl}_2\text{O}_9$  ( $\text{MH}^+$ ): 641.1781. Found: 641.1735. Accurate mass calculated for  $\text{C}_{28}\text{H}_{34}\text{N}_4\text{Cl}_2\text{O}_9\text{Na}$  ( $\text{Mna}^+$ ): 663.1601. Found: 663.1542.

[3S(1S,9S)] t-Butyl 3-(9-benzyloxycarbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-oxopentanoate (216d), was synthesized from 215d by the same method as compound 216e to afford 216d as a white glassy solid (688mg, 68%): mp 90-170  $^{\circ}\text{C}$ ;  $[\alpha]_{\text{D}}^{25}$  -83.4 (c 1.01,  $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3338, 2933, 1736, 1670, 1525, 1433, 1417, 1368, 1258, 1151, 1056, 1031;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.33 (8H, m), 7.18 (1H, d), 5.65 (1H, d), 5.19 (1H, m), 5.09 (2H, s), 4.98-4.86 (1H, m), 4.82-4.49 (2H, d), 3.30-3.07 (1H, m), 3.05-2.59 (4H, m), 2.42-2.27 (1H, m), 2.18-1.59 (5H, m), 1.42 (9H, s); MS (ES $-$ ) 737/5/3 (M, 13%), 185 (100).

[3S(1S,9S)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-oxopentanoate (216e). Dess-Martin reagent (3.82g; 9.0mmol) was added to a stirred solution of the alcohol 215e (3.17g; 4.5mmol) in

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CH<sub>2</sub>Cl<sub>2</sub> (100ml). The mixture was stirred for 1h, diluted with EtOAc (300ml), then washed with a 1:1 mixture of sat. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and sat. NaHCO<sub>3</sub> (100ml) followed by brine (100ml). The mixture was dried (MgSO<sub>4</sub>) then

- 5 concentrated. The residue was purified by flash chromatography to afford 2.2g (70%) of **216e** as a colourless solid: mp 102-107 °C;  $[\alpha]_D^{32}$  -82.5 (c 0.1, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3374, 2937, 1739, 1661, 1525, 1433, 1275, 1260, 1152; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.85-7.78 (2H, m),  
10 7.57-7.32 (6H, m), 7.09 (1H, d, J = 7.9), 7.01 (1H, d, J 7.3), 5.25-5.16 (1H, m), 5.16-5.05 (1H, m), 5.15 (1H, d), 5.03 (1H, d), 4.99-4.90 (1H, m), 4.68-4.54 (1H, m), 3.31-3.17 (1H, m), 3.17-2.72 (4H, m), 2.45-2.35 (1H, m), 2.30-1.66 (5H, m), 1.44 (9H, s); Anal. Calcd for  
15 C<sub>33</sub>H<sub>36</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>9</sub> · 0.5H<sub>2</sub>O: C, 55.62; H, 5.23; N, 7.86; Cl, 9.95. Found: C, 55.79; H, 5.15; N, 7.80; Cl 9.81. MS (ES +) 729/7/5 (M + Na), 707/5/3 (M + 1), 163 (100%).

- [**3S(1S,9S)**] 3-(9-Acetylamino-6,10-dioxo-  
1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-  
20 [1,2-a][1,2]diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-oxopentanoic acid (**217c**), was synthesized from **216c** by the same method as compound **217e** as a glassy white solid (166mg, 66%): mp  
85-175 °C;  $[\alpha]_D^{25}$  -156 (c 0.13, MeOH); IR (KBr) 3373,  
25 2929, 1742, 1659, 1562, 1533, 1433, 1412, 1274, 1266, 1223, 1197, 1145, 1138; <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.38 (3H, s), 5.14-5.03 (1H, m), 4.49-4.32 (2H, m), 3.50-3.27 (1H, m), 3.11-2.92 (1H, m), 2.84-2.62 (2H, m), 2.46-2.11 (2H, m), 2.05-1.46 (5H, m), 1.92 (3H, s); Anal. Calcd  
30 for C<sub>24</sub>H<sub>26</sub>N<sub>4</sub>Cl<sub>2</sub>O<sub>9</sub> · H<sub>2</sub>O: C, 47.77; H, 4.68; N, 9.29. Found: C, 47.75; H, 4.59; N, 9.07. MS (ES +) 627/5/3 (M+K, 21%), 611/9/7 (M+Na, 87), 589/7/5 (M<sup>+</sup> +1, 71),

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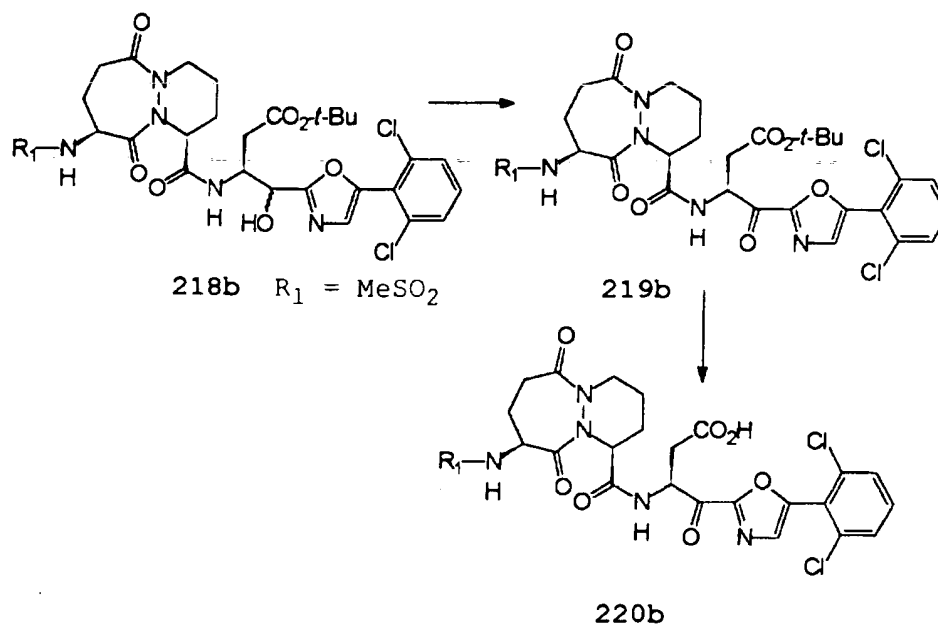
266 (100); Accurate mass calculated for  $C_{24}H_{27}N_4Cl_2O_9$  ( $MH^+$ ): 585.1155. Found: 585.1134.

[3S(1S,9S)] 3-(9-Benzoyloxycarbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-oxopentanoic acid (217d), was synthesized from 216d by the same method as compound 217e to afford 217d as a white glassy solid (310mg, 96%): mp 85-110 °C;  $[\alpha]_D^{24}$  -85.9 (c 0.13, MeOH); IR (KBr) 3351, 2945, 1738, 1669, 1524, 1433, 1258, 1147, 1057;  $^1H$  NMR ( $CD_3OD$ )  $\delta$  7.56 (4H, m), 7.45 (5H, m), 5.32 (2H, m), 5.20 (2H, s), 4.76-4.48 (3H, m), 3.65-3.38 (3H, m), 3.27-3.09 (2H, m), 3.03-2.89 (2H, m), 2.65-2.24 (3H, m), 2.19-1.62 (5H, m); MS (ES -) 679/7/5 (M-1, 100%); Accurate mass calculated for  $C_{30}H_{31}N_4Cl_2O_{10}$  ( $MH^+$ ): 677.1417. Found: 677.1430.

[3S(1S,9S)] 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-(2,6-dichlorobenzoyloxy)-4-oxopentanoic acid (217e), TFA (25ml) was added dropwise to an ice cold stirred solution of the ester 216e (2.11g, 3.0mmol). The mixture was stirred at 0 °C for 20min then at room temperature for 1h. The mixture was evaporated to dryness then coevaporated with ether three times. Addition of dry ether (50 ml) and filtration afforded 1.9g (98%) of 217e as a colourless solid: mp 126-130 °C;  $[\alpha]_D^{30}$  -122.0 (c 0.1, MeOH); IR (KBr) 3322, 1740, 1658, 1651, 1532, 1433, 1277, 1150;  $^1H$  NMR ( $D_6$ -DMSO)  $\delta$  8.87 (1H, d,  $J$  = 7.4), 8.61 (1H, d,  $J$  = 7.8), 7.92-7.86 (2H, m), 7.65-7.43 (6H, m), 5.25-5.12 (3H, m), 4.94-4.60 (2H, m), 4.44-4.22 (1H, m),

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3.43-3.10 (1H, m), 3.00-2.52 (3H, m), 2.45-2.10 (3H, m), 2.10-1.75 (2H, m), 1.75-1.50 (2H, m); Anal. Calcd for  $C_{29}H_{28}Cl_2N_4O_9 \cdot 1H_2O$ : C, 52.34; H, 4.54; N, 8.42; Cl, 10.66. Found: C, 52.02; H, 4.36; N, 8.12; Cl, 10.36. MS (ES<sup>-</sup>) 649/7/5 (M - 1), 411 (100%).



[3*S*,4*RS*(1*S*,9*S*)] *t*-Butyl 4-[5-(2,6-dichlorophenyl)-oxazol-2-yl]-3-(6,10-dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-*a*][1,2]diazepine-1-carboxamido)-4-hydroxybutanoate (218b), was prepared from the acid 212b and 99 in an analogous way to compound 215e to afford a mixture of diastereomers (865mg, 80%) as a colourless solid: IR (KBr) 3298, 2974, 1723, 1659, 1544, 1518, 1430, 1394, 1370, 1328, 1273, 1256, 1156, 1134; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.45-7.28 (4H, m), 7.26-7.15 (2H, m), 5.26-5.10 (2H, m), 4.80-4.67 (1H, m), 4.59-4.42 (2H, m), 3.32-3.17 (1H, m), 2.96 (3H, 2xs), 2.93-2.79 (1H, m), 2.71-2.53

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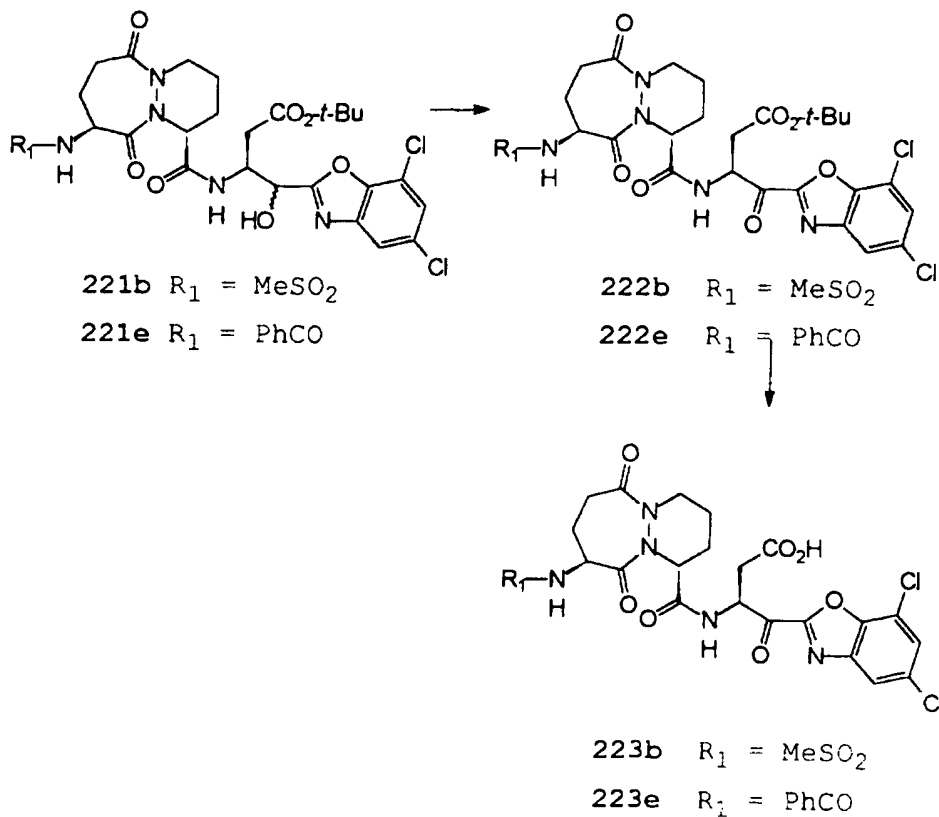
(4H, m), 2.38-2.28 (1H, m), 2.07-1.81 (4H, m); Anal. Calcd for  $C_{28}H_{35}N_5Cl_2O_9S \cdot 0.5 H_2O$ : C, 48.21; H, 5.20; N, 10.03. Found: C, 48.35; H, 5.26; N, 9.48. MS (ES<sup>+</sup>) 714/2/0 ( $M + Na$ , 25%), 692/90/88 ( $M^+ + 1$ , 51), 636/4/2 (38), 246 (100). Accurate mass calculated for  $C_{28}H_{36}N_5Cl_2O_9S (MH^+)$ : 688.1611. Found: 688.1615.

[3S(1S,9S)]t-Butyl 4-[5-(2,6-dichlorophenyl)-oxazol-2-yl]-3-(6,10-dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoate (219b), was prepared from 218b in an analogous way to compound 216e as an off-white powder (675mg, 81%): mp 100-200 °C;  $[\alpha]_D^{24} -84.9$  (c 1.01,  $CH_2Cl_2$ ); IR (KBr) 3336, 2978, 2936, 1719, 1674, 1510, 1433, 1421, 1369, 1329, 1274, 1257, 1155, 991, 789;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.47-7.38 (4H, m), 7.24 (1H, d), 5.61-5.53 (1H, m), 5.48 (1H, d), 5.38-5.30 (1H, m), 4.67-4.45 (2H, m), 3.48-3.18 (2H, m), 3.04-2.90 (2H, m), 2.97 (3H, s), 2.69-2.54 (1H, m), 2.42-2.32 (1H, m), 2.22-2.15 (1H, m), 2.07-1.93 (3H, m), 1.71-1.65 (2H, m), 1.38 (9H, s); Anal. Calcd for  $C_{28}H_{33}N_3Cl_2O_9S$ : C, 48.98; H, 4.84; N, 10.20; S, 4.67. Found: C, 48.73; H, 4.95; N, 9.65; S, 4.54. MS (ES<sup>+</sup>) 692/90/88 ( $M^+ + 1$ , 100%), 636/4/2 (71). Accurate mass calculated for  $C_{28}H_{34}N_5Cl_2O_9S (MH^+)$ : 686.1454. Found: 686.1474.

[3S(1S,9S)] 4-[5-(2,6-Dichlorophenyl)oxazol-2-yl]-3-(6,10-dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (220b), was prepared from 219b in an analogous way to compound 217e as a pale cream powder (396mg, 87%): mp 100-200 °C;  $[\alpha]_D^{27} -$

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129 (c 0.12, MeOH); IR (KBr) 3310, 3153, 1713, 1667, 1557, 1510, 1432, 1421, 1329, 1273, 1258, 1221, 1193, 1153, 1134, 992, 789;  $^1\text{H}$  NMR ( $d^6$  DMSO)  $\delta$  7.88 (1H, s), 7.81-7.60 (4H, m), 5.49-5.28 (1H, m), 5.24-5.14 (1H, m), 4.46-4.22 (2H, m), 3.30-3.03 (2H, m), 2.97-2.76 (3H, m), 2.96 (3H, s), 2.46-2.24 (1H, m), 2.16-2.05 (1H, m), 2.03-1.78 (3H, m), 1.68-1.46 (2H, m); MS (ES-) 632/30/28 (M - 1, 68%), 149/7/5 (100). Accurate mass calculated for  $\text{C}_{24}\text{H}_{26}\text{N}_5\text{Cl}_2\text{O}_9\text{S}$  ( $\text{MH}^+$ ): 630.0828. Found: 630.0852.



15 [3*S*,4*RS*(1*S*,9*S*)] *t*-Butyl 4-(5,7-dichlorobenzoxazol-2-yl)-3-(6,10-dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino-

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[1,2-a][1,2]diazepine-1-carboxamido)-4-hydroxybutanoate (221b), was prepared from the acid 212b and (3S,4RS) t-butyl N-(allyloxycarbonyl)-3-amino-4-hydroxy-4-(5,7-dichlorobenzoxazol-2-yl)butanoate (204) by an analogous method as that used for compound 215e to afford a mixture of diastereomers (460mg, 70%) as a glass: IR (film) 3325, 1725, 1664, 1453, 1399, 1373, 1327, 1274, 1256, 1155; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.57 (1H, m), 7.36 (2H, m), 6.06 (1H, t), 5.29 (2H, m), 4.79 (1H, m), 4.47 (1H, m), 3.23 (1H, m), 2.97 and 2.94 (3H combined, 2 x s), 2.9-2.4 (4H, m), 2.30 (1H, m), 1.96 (4H, m), 1.41 and 1.37 (9H combined, 2 x s). MS ES Da/e 660 (M - 1)<sup>-</sup> Cl<sup>35</sup> 100%, 662 (M - 1)<sup>-</sup> Cl<sup>37</sup>.

[3S,4RS(1S,9S)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-4-(5,7-dichlorobenzoxazol-2-yl)-4-hydroxybutanoate (221e), was prepared from the acid (212e) and (3S,4RS) t-butyl N-(allyloxycarbonyl)-3-amino-4-hydroxy-4-(5,7-dichlorobenzoxazol-2-yl)butanoate (204) by an analogous method as that used for compound 215e to afford a mixture of diastereomers (613mg, 87%) as a glass: IR (film) 3328, 1729, 1660, 1534, 1454, 1422, 1399, 1276, 1254, 1155; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.80 (2H, d), 7.60-7.35 (5H, m), 7.05 (2H, m), 5.13 (3H, m), 4.74 (1H, m), 4.51 (1H, m), 3.25 (1H, m), 3.1-2.6 (5H, m), 2.33 (1H, m), 2.1-1.5 (5H, m), 1.43 and 1.41 (9H combined, 2 x s). MS ES<sup>+</sup> Da/e 688 (M + 1)<sup>+</sup> Cl<sup>35</sup> 55%, 690 (M + 1)<sup>+</sup> Cl<sup>37</sup> 35%, 328 100%.

[3S(1S,9S)] t-Butyl 4-(5,7-dichlorobenzoxazol-2-yl)-3-(6,10-dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-



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octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoate (222b), was prepared from 221b by an analogous method as that used for compound 216e to afford a colourless glass (371mg, 86%):  $[\alpha]_D^{26}$  -81.0 (c 0.1, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3324, 2979, 2936, 1726, 1664, 1394, 1370, 1328, 1155, 991; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.78 (1H, d), 7.57 (2H, m), 5.87 (1H, d), 5.69 (1H, m), 5.47 (1H, m), 4.55 (2H, m), 3.24 (2H, m), 3.0 (5H, m + s), 2.59 (1H, m), 2.39 (1H, m), 2.2 - 1.7 (4H, m), 1.65 (1H, m), 1.40 (9H, s).

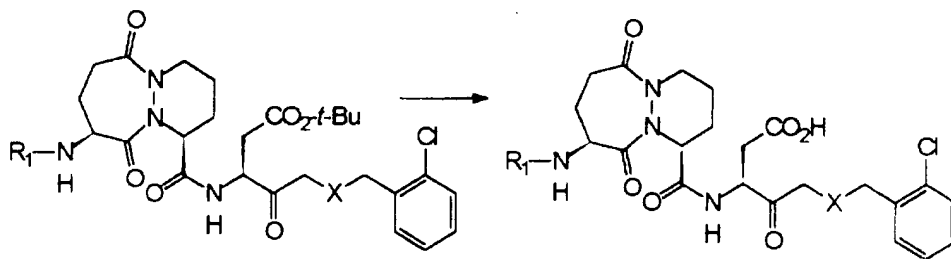
[3S(1S,9S)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-4-(5,7-dichlorobenzoxazol-2-yl)-4-oxobutanoate (222e), was prepared from 221e by an analogous method as that used for compound 216e to afford a colourless glass (480mg, 84%):  $[\alpha]_D^{25}$  -86.4 ° (c 0.1 CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3337, 2978, 2938, 1728, 1657, 1534, 1456, 1422, 1395, 1370, 1277, 1250, 1154; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.80 (3H, m), 7.50 (4H, m), 7.20 (1H, d), 7.02 (1H, d), 5.60 (1H, m), 5.28 (1H, m), 5.15 (1H, m), 4.11 (1H, m), 3.34 (2H, m), 2.96 (3H, m), 2.40 (1H, m), 2.20 (1H, m), 1.92 (2H, m), 1.67 (2H, m), 1.38 (9H, s). MS ES<sup>-</sup> Da/e 684 (M - 1)<sup>-</sup> Cl<sup>35</sup> 47%, 686 (M - 1)<sup>-</sup> Cl<sup>37</sup> 32%.

[3S(1S,9S)] 4-(5,7-Dichlorobenzoxazol-2-yl)-3-(6,10-dioxo-9-methylsulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (223b), was prepared from 222b by an analogous method as that used for compound 217e to afford an off-white solid (257mg, 78%):  $[\alpha]_D^{25}$  -105.7 ° (c 0.1, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3321,

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1723, 1663, 1407, 1325, 1151, 992;  $^1\text{H}$  NMR ( $\text{D}_6\text{-DMSO}$ )  $\delta$  8.96 (1H, d), 8.18 (1H, d), 7.96 (1H, d), 5.50 (1H, m), 5.15 (1H, m), 4.30 (2H, m), 3.06 (2H, m), 2.87 (5H, m + s), 2.29 (1H, m), 1.99 (4H, m), 1.56 (2H, m).

5 **[3S(1S,9S)] 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido)-4-(5,7-dichlorobenzoxazol-2-yl)-4-oxobutanoic acid (223e)**, was prepared from **222e** by an analogous method as that used  
 10 for compound **217e** to afford a pale cream solid (311mg, 78%): mp 167-180 °C;  $[\alpha]_{\text{D}}^{23}$  -88.6 ° (c 0.1  $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3331, 1724, 1658, 1534, 1458, 1421, 1279, 1256, 991;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.77 (4H, m), 7.4 (5H, m), 5.57 (1H, bs), 5.33 (1H, bs), 5.47 (1H, q), 4.56 (1H, bd),  
 15 3.60 (2H, m), 3.20 (3H, m), 2.76 (1H, m), 2.36 (1H, dd), 2.0 (3H, m), 1.66 (1H, m). MS ES Da/e 628 ( $\text{M} - 1$ ) $^-$   $\text{Cl}^{35}$  7%, 630 ( $\text{M} - 1$ ) $^-$   $\text{Cl}^{37}$  2.3%, 584 100%.



**224e**  $\text{R}_1 = \text{PhCO}$ ,  $\text{X} = \text{S}$

**225e**  $\text{R}_1 = \text{PhCO}$ ,  $\text{X} = \text{O}$

**226e**  $\text{R}_1 = \text{PhCO}$ ,  $\text{X} = \text{S}$

**227e**  $\text{R}_1 = \text{PhCO}$ ,  $\text{X} = \text{O}$

20 **[3S(1S,9S)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-(2-chlorophenyl)methylthio-4-oxopentanoate (224e)**. 1-Hydroxybenzotriazole (0.23g,

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1.71mmol) and ethyl dimethylaminopropyl carbodiimide hydrochloride was added to a stirred solution of the acid **212e** (0.295g, 0.853mmol) in THF (5ml). After 5min water (0.5ml) was added followed, after a further 7min, by the addition of a solution of (3S) t-butyl-3-allyloxycarbonylamino-5-(2-chloro-phenyl)methylthio-4-oxopentanoate (**123**, 0.478g, 1.02mmol) and (PPh<sub>3</sub>)<sub>2</sub>PdCl<sub>2</sub> (20mg) in THF (2ml). Tributyltin hydride (0.65ml, 2.33mmol) was added dropwise during 20min. The mixture was kept for 4.5h then diluted with EtOAc, washed with 1M HCl, brine, sat. aq. NaHCO<sub>3</sub> and then brine again. The mixture was dried (MgSO<sub>4</sub>) and concentrated. The residue was triturated several times with hexane, which was decanted and discarded, then purified by flash chromatography (10-100% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>) to afford 0.2g (35%) of a white glassy solid: mp 70-72 °C; [α]<sub>D</sub><sup>26</sup> - 82.5 ° (c 0.02, CH<sub>2</sub>Cl<sub>2</sub>). IR (KBr) 3404, 1726, 1660, 1534, 1524, 1422, 1277, 1254, 1154; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.83-7.78 (2H, m), 7.7, 7.75-7.32, 7.26-7.20 (7H, 3m), 7.12 (1H, d, J = 8.2), 7.01 (1H, d, J = 7.3), 5.23-5.08 (2H, m), 5.03-4.94 (1H, m), 4.62 (1H, dt, J = 14.5), 3.78 (2H, m), 3.38-3.29 (1H, m), 3.26 (2H, s), 3.06-2.82 (4H, m), 2.71 (1H, dd, J = 17.2, 4.5), 2.39 (1H, dd, J = 13.2, 6.5), 2.15-1.83, 1.73-1.63 (5H, m), 1.45 (9H, s). Anal. Calcd for C<sub>33</sub>H<sub>39</sub>ClN<sub>4</sub>O<sub>7</sub>S: C, 59.05; H, 5.86; N, 8.35. Found: C, 59.00; H, 5.80; N, 7.92.

[3RS, (1S,9S)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-(2-chlorophenylmethyloxy)-4-oxopentanoate (**225e**), was prepared from acid **212e** and (3S) t-butyl N-(allyloxycarbonyl)-3-amino-5-(2-chlorophenylmethyloxy)-4-oxopentanoate (**201**) using a

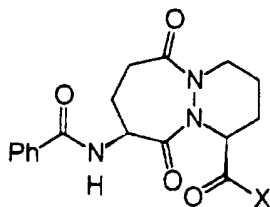
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method similar to that used for compound **224e**, to afford 40mg (23%) of a glassy solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.83-7.73 (2H, m), 7.67-7.10 (9H, m), 5.23-5.09 (2H, m), 4.59 (1H, m), 4.45-4.22 (2H, m), 3.7-3.19, 3.08-2.72, 2.71-2.47, 2.05-1.85, 1.72-1.61, 1.45-1.26 (20H, 6m).

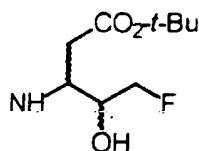
[3S(1S,9S)] 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-(2-chlorophenyl)methylthio-4-oxopentanoic acid (**226e**), was prepared from **224e** by an analogous method as that used for compound **217e** which afforded 0.22g (81%) of an off-white solid: mp 95-100 °C;  $[\alpha]_D^{23}$  -95.6 ° (c 0.2,  $\text{CH}_2\text{Cl}_2$ ). IR (KBr) 3393, 1720, 1658, 1529, 1422, 1279;  $^1\text{H}$  NMR ( $\text{D}_6$ -DMSO)  $\delta$  8.80 (1H, d,  $J$  = 7.5), 7.89 (2H, m), 7.7 (1H, d,  $J$  = 7.7), 7.56-7.28 (7H, m), 5.10 (1H, m), 4.87-4.73 (2H, m), 4.39 (1H, m), 3.77 (2H, m), 3.44, 3.35 (2H, + $\text{H}_2\text{O}$ , 2m), 2.97-2.56, 2.2, 1.92, 1.61 (11H, 4m). Anal. Calcd for  $\text{C}_{29}\text{H}_{31}\text{ClN}_4\text{O}_7\text{S} \cdot 0.5\text{H}_2\text{O}$ : C, 55.02; H, 5.10; N, 8.85. Found: C, 55.00; H, 5.09; N, 8.71.

[3RS, (1S,9S)] 3-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-(2-chlorophenylmethoxy)-4-oxopentanoic acid (**227e**), was prepared from **225e** by an analogous method as that used for compound **217e**. The product was further purified by flash chromatography (0-5% MeOH/ $\text{CH}_2\text{Cl}_2$ ) to afford 19mg (81%) of a glassy solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.79 (2H, m), 7.66-7.18 (9H, m), 5.30-5.10 (2H, m), 4.85 (1H, m), 4.65 (2H, m), 4.53 (1H, m), 4.28 (2H, m), 3.28, 3.01, 2.72, 2.33, 1.94, 1.60 (11H, 6m). MS ( $\text{ES}^-$ , m/z) 597 ( $\text{M}^+ - 1$ , 100%).

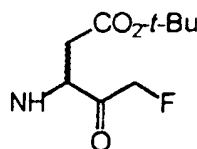
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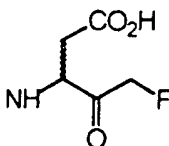
228e X =



229e X =



230e X =



[3*RS*,4*RS*(1*S*,9*S*)] *t*-Butyl 3-(9-benzoylamino-6,10-dioxo-  
 5 1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino-  
 [1,2-*a*][1,2]-diazepine-1-carboxamido)-5-fluoro-4-  
 (228e). 1-Hydroxybenzotriazole (0.23g, 1.68mmol)  
 followed by ethyldimethylaminopropyl carbodiimide  
 hydrochloride (0.21g, 1.09mmol) were added to a stirred  
 10 solution of the acid **212e** (0.29g, 0.84mmol) in CH<sub>2</sub>Cl<sub>2</sub>  
 (3ml) at rt. The mixture was kept for 10min then a  
 solution of (3*RS*,4*RS*) *t*-butyl 3-amino-5-fluoro-4-  
 hydroxypentanoate (Revesz, L. et al. Tetrahedron Lett.,  
 52, pp. 9693-9696 (1994); 0.29g, 1.40mmol) in CH<sub>2</sub>Cl<sub>2</sub>  
 15 (3ml) was added followed by 4-dimethylaminopyridine

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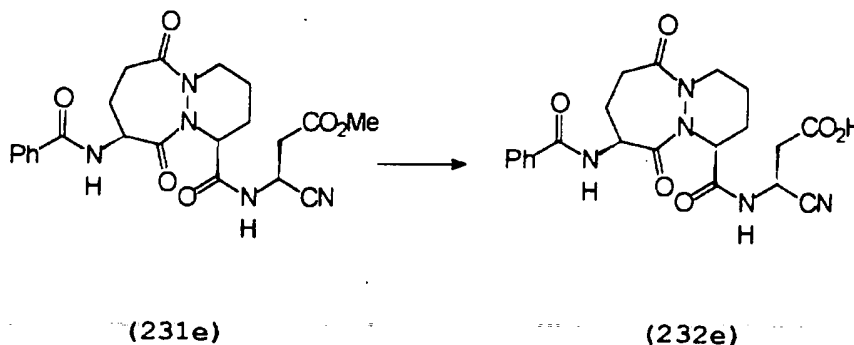
(10mg). The solution was stirred for 17h, diluted with EtOAc, washed with 1M HCl, brine, sat. aq. NaHCO<sub>3</sub> and brine again, dried (MgSO<sub>4</sub>) and concentrated. The residue was purified by flash chromatography (50-100% EtOAc/CH<sub>2</sub>Cl<sub>2</sub> and 5% MeOH/EtOAc) to afford 0.25g (56%) of a white glassy solid: IR (KBr) 3343, 1726, 1658, 1536, 1426, 1279, 1257, 1157; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.84-7.79 (2H, m), 7.57-7.40 (3H, m), 7.05-6.92, 6.73 (2H, 2m), 5.17-5.04 (2H, m), 4.56, 4.35-4.21, 4.04 (5H, 3m), 3.36, 3.09-2.34, 2.00 (11H, 3m), 1.46 (9H, s). Anal. Calcd for C<sub>26</sub>H<sub>35</sub>N<sub>4</sub>O<sub>7</sub> · 0.5H<sub>2</sub>O: C, 57.45; H, 6.65; N, 10.31. Found: C, 57.64; H, 6.56; N, 10.15.

[3RS,4RS(1S,9S)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]-diazepine-1-carboxamido)-5-fluoro-4-oxypentanoate (229e) was prepared from 228c by an analogous method to that used for compound 216e. After purification by flash chromatography (30-50% EtOAc/CH<sub>2</sub>Cl<sub>2</sub>) the product was obtained as a white glassy solid (0.194g, 89%): IR (KBr) 3376, 1728, 1659, 1529, 1424, 1279, 1256, 1156.

[3RS, (1S,9S)] 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-5-fluoro-4-oxopentanoic acid (230e), was prepared from 229e by an analogous method to that used for compound 217e to afford 230e as a white glassy solid (100%): mp 105-125 °C; [α]<sub>D</sub><sup>23</sup> -91.4 ° (c 0.72, CH<sub>3</sub>OH). IR (KBr) 3336, 1789, 1737, 1659, 1535, 1426, 1279, 1258, 1186; <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.71-7.68 (2H, m), 7.37-7.23 (3H, m), 5.02, 4.88-4.63,

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4.37-4.0 (6H, 3m), 3.30, 2.97, 2.68-2.60, 2.37-1.54 (11H, 4m). MS (ES<sup>-</sup>, m/z) 475 (M<sup>+</sup> - 1, 100%).



[3S(1S,9S)]-Methyl 9-(benzoylamino)-3-[6,10-dioxo-  
 5 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-  
 [1,2-a][1,2]diazepine-1-carboxamido]-3-cyanopropanoate  
 (231e). N-Fluorenylmethyloxy-carbonyl-3-amino-3-  
 cyanopropionic acid methyl ester (EP0547699A1, 385mg,  
 1.1mmol) was treated with 17ml of diethylamine. After  
 10 1.5h stirring at room temperature the solution was  
 concentrated. The residue was chromatographed on  
 silica gel (3% methanol in CH<sub>2</sub>Cl<sub>2</sub>) and gave the free  
 amine as a pale yellow oil. To a solution of this oil  
 and hydroxybenzotriazole (297mg, 2.19mmol) in DMF  
 15 (5ml), was added at 0 °C ethyldimethylaminopropyl  
 carbodiimide (232mg, 1.21mmol, 1.1 equiv) followed by  
 (1S,9S) 9-(benzoylamino)-[6,10-dioxo-1,2,3,4,7,8,9,10-  
 octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-  
 carboxylic acid (212e). After stirring at 0 °C for 5  
 20 min and then at room temperature overnight, the mixture  
 was diluted with CH<sub>2</sub>Cl<sub>2</sub> (50ml) and the resulting  
 solution washed successively with 1M HCl (2 x 30ml),  
 H<sub>2</sub>O (30ml), 10% NaHCO<sub>3</sub> (2 x 30ml) and sat. aq. NaCl,  
 dried (MgSO<sub>4</sub>) and concentrated. Purification by flash

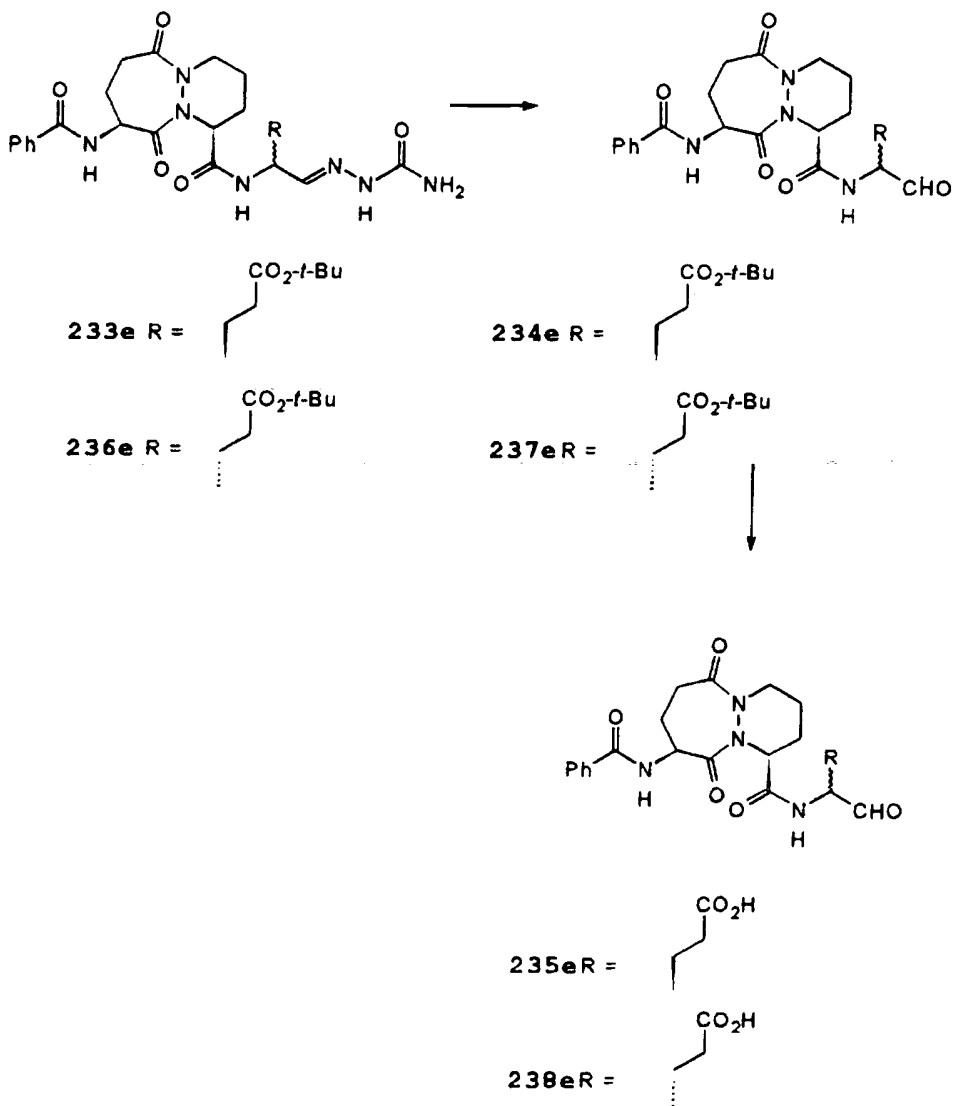
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chromatography on silica gel (3% methanol in CH<sub>2</sub>Cl<sub>2</sub>) afforded the compound **231e** (404mg, 83%) as a solid:  $[\alpha]_D^{20}$  -121 ° (c 0.14, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.40-7.83 (5H, m), 7.38 (1H, d), 6.96 (1H, d), 5.27-5.07 (2H, m), 4.66-4.50 (1H, m), 3.79 (3H, s), 3.23-2.73 (6H, m), 2.47-2.33 (1H, m), 2.15-1.82 (4H, m); Anal. Calcd for C<sub>22</sub>H<sub>25</sub>N<sub>5</sub>O<sub>6</sub>: C, 58.0; H, 5.53; N, 15.38. Found: C, 57.6; H, 5.6; N, 15.0.

**[3S(1S,9S)] 9-(Benzoylamino)-3-[6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamido]-3-cyanopropanoic acid (232e)**. A solution of methyl ester **231e** (400mg, 0.88mmol) in methanol (30ml) and water (30ml) was cooled at 0 °C and treated with diisopropylethylamine. The solution was stirred at 0 °C for 10min and then at room temperature overnight. The heterogeneous mixture was concentrated and the solid obtained was chromatographed on silica gel (5% methanol/1% formic acid in CH<sub>2</sub>Cl<sub>2</sub>) affording the free acid **232e** (170mg, 44%) as a white solid: mp 155 °C (dec);  $[\alpha]_D^{20}$  -117 ° (c 0.1, MeOH); IR (KBr) 3343, 3061, 2955, 1733, 1656, 1577, 1533, 1490, 1421, 1342, 1279, 1256, 1222, 1185, 708; <sup>1</sup>H NMR (D<sup>4</sup>-MeOH) δ 7.88-7.28 (5H, m), 5.20-5.03 (1H, m), 4.98-4.84 (2H, m), 4.75-4.53 (1H, m), 4.51-4.34 (1H, m), 3.45-3.22 (1H, m), 3.14-2.94 (1H, m), 3.14-2.94 (1H, m), 2.88-2.61 (2H, m), 2.53-1.50 (8H, m); Anal. Calcd for C<sub>21</sub>H<sub>23</sub>N<sub>5</sub>O<sub>6</sub> · 1.5H<sub>2</sub>O: C, 53.84; H, 5.59; N, 14.95; O, 25.61. Found: C, 54.3; H, 5.4; N, 14.3.



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[4*S*, (1*S*,9*S*)] *t*-Butyl 4-[9-(benzoylamino)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino-[1,2-*a*][1,2]diazepine-1-carboxamido]-5-oxopentanoate semicarbazone (233e). A solution of (1*S*,9*S*) 6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-9-(benzoylamino)-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxylic acid (212e) (345mg, 1.0mmol), (4*S*) *t*-butyl *N*-

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(allyloxycarbonyl)-4-amino-5-oxopentanoate semicarbazone (**208a**) (361mg, 1.1mmol, 1.1 equiv) and  $(\text{Ph}_3\text{P})_2\text{PdCl}_2$  (20mg) in  $\text{CH}_2\text{Cl}_2$  (5ml), was treated dropwise with  $n\text{-Bu}_3\text{SnH}$  (0.621ml, 2.3mmol, 2.1 equiv).

5 The resulting orange brown solution was stirred at 25 °C for 10min and then 1-hydroxybenzotriazole (297mg, 2.2mmol, 2 equiv) was added. The mixture was cooled to 0 °C and ethyldimethylaminopropyl carbodiimide (253mg, 1.3mmol, 1.2 equiv) added. After stirring at 0 °C for

10 10min and then at room temperature overnight, the mixture was diluted with EtOAc (50ml) and the resulting solution washed successively with 1M HCl (3 x 25ml), 10%  $\text{NaHCO}_3$  (3 x 25ml) and sat. aq. NaCl, dried ( $\text{MgSO}_4$ ) and concentrated. Flash chromatography on silica gel

15 (2-10% methanol in  $\text{CH}_2\text{Cl}_2$ ) afforded compound **233e** (280mg, 49%) as a tan solid:  $[\alpha]_{\text{D}}^{20} -95$  (c 0.09, MeOH); IR (KBr) 3477, 3333, 2968, 2932, 1633, 1580, 1535, 1423, 1378, 1335, 1259, 1156, 1085, 709;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  9.32 (1H, s), 7.83-7.39 (6H, m), 7.11-7.09 (1H, m),

20 6.30-5.30 (2H, brs), 5.17-5.05 (2H, m), 4.62-4.38 (2H, m), 3.30-3.15 (1H, m), 3.13-2.65 (2H, m), 2.46-2.19 (3H, m), 2.15-1.54 (8H, m), 1.42 (9H, s).

[**4R**, (**1S**,**9S**)] *t*-Butyl 4-[9-(benzoylamino)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-

25 [1,2-a][1,2]diazepine-1-carboxamido]-5-oxopentanoate semicarbazone (**236e**), was prepared by an analogous method to that used for **233e** using (**4R**) *t*-butyl *N*-allyloxycarbonyl-4-amino-5-oxo-pentanoate semicarbazone (**208b**, 435mg, 1.33mmol). The product was obtained as a

30 foam (542mg, 71%):  $[\alpha]_{\text{D}}^{20} -99$  ° (c 0.19,  $\text{CHCl}_3$ ); IR (KBr) 3473, 3331, 3065, 2932, 2872, 1660, 1580, 1533, 1488, 1423, 1370, 1337, 1278, 1254, 1223, 1155, 1080,

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1024, 983, 925, 877, 846, 801, 770, 705;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  
 $\delta$  9.42 (1H, s), 7.81 (2H, d), 7.51-7.40 (4H, m), 7.06  
(1H, d), 6.50-5.50 (2H, broad s), 5.25-5.00 (2H, m),  
4.60-4.45 (2H, m), 3.15-2.85 (2H, m), 2.75-2.35 (1H,  
5 m), 2.30-1.23 (11H, m), 1.42 (9H, s).

[4S, (1S,9S)] t-Butyl 4-[9-(benzoylamino)-6,10-dioxo-  
1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-  
[1,2-a][1,2]diazepine-1-carboxamido]-5-oxopentanoate  
(234e). A solution of semicarbazone 233e (390mg,  
10 0.68mmol) in methanol (10ml) was cooled at 0 °C and  
then treated with a 38% aq. solution of formaldehyde  
(2ml) and 1M HCl (2ml). The reaction mixture was then  
stirred overnight at room temperature. The solution  
was concentrated to remove the methanol. The aq.  
15 solution was extracted with EtOAc (30ml). The organic  
solution was successively washed with 10%  $\text{NaHCO}_3$  (30ml)  
and sat. aq. NaCl (30ml), dried ( $\text{MgSO}_4$ ) and  
concentrated. Purification by flash chromatography on  
silica gel (2-5% methanol in  $\text{CH}_2\text{Cl}_2$ ) afforded 234e  
20 (179mg, 51%) as a white foam:  $[\alpha]_{\text{D}}^{20}$  -101 ° (c 0.064,  
MeOH); IR (KBr) 3346, 2976, 2934, 1730, 1657, 1535,  
1456, 1425, 1278, 1255, 1156, 708;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$   
9.56 (1H, s), 7.88-7.38 (5H, m), 7.01 and 6.92 (2H,  
2d), 5.27-5.08 (2H, m), 4.69-4.46 (1H, m), 3.50-3.27  
25 (2H, m), 3.15-2.73 (2H, m), 2.46-1.83 (10H, m), 1.45  
(9H, s).

[4R, (1S,9S)] t-Butyl 4-[9-(benzoylamino)-6,10-dioxo-  
1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-  
[1,2-a][1,2]diazepine-1-carboxamido]-5-oxopentanoate  
30 (237e), was prepared from 236e by an analogous method  
to 234e to afford a white foam (390mg, 85%):  $[\alpha]_{\text{D}}^{20}$

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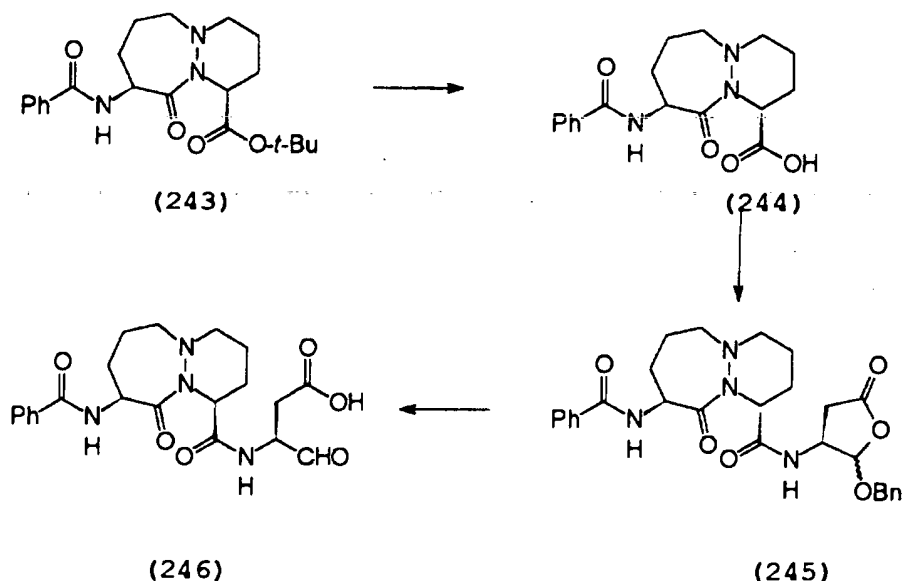
-113 ° (c 0.242, CHCl<sub>3</sub>); IR (KBr) 3352, 3065, 2974, 1729, 1657, 1536, 1489, 1454, 1423, 1369, 1338, 1278, 1255, 1223, 1156, 1078, 1026, 981, 846, 709.

[4S, (1S,9S)] 4-[9-(Benzoylamino)-6,10-dioxo-  
5 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-  
[1,2-a][1,2]diazepine-1-carboxamido]-5-oxopentanoic  
acid (235e). A solution of t-butyl ester 234e (179mg, 0.35mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (3ml) was cooled to 0 °C and treated with trifluoroacetic acid (2ml). The resulting  
10 solution was stirred at 0 °C for 30min and then at room temperature for 2h. The solution was concentrated, the residue taken up in dry CH<sub>2</sub>Cl<sub>2</sub> (5ml) and the mixture again concentrated. This process was repeated once again with more CH<sub>2</sub>Cl<sub>2</sub> (5ml). The residue obtained was  
15 crystallized in diethyl ether. The precipitate was collected and purified on silica gel column (5% methanol in CH<sub>2</sub>Cl<sub>2</sub>) which afforded compound 235e as a white solid (111mg, 70%): mp 142 °C (dec); [α]<sub>D</sub><sup>20</sup> -85.5 (c 0.062, MeOH); IR (KBr) 3409, 3075, 2952, 1651, 1541, 1424, 1280, 1198, 1136, 717; <sup>1</sup>H NMR (D<sub>6</sub>-DMSO) δ 9.40 (1H, s), 8.62 (2H, m), 7.96-7.38 (5H, m), 5.19-5.02 (1H, m), 4.98-4.79 (1H, m), 4.48-4.19 (1H, m), 3.51-3.11 (2H, m), 3.04-2.90 (2H, m), 2.38-1.46 (10H, m).

[4R, (1S,9S)] 4-[9-(Benzoylamino)-6,10-dioxo-  
25 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-  
[1,2-a][1,2]diazepine-1-carboxamido]-5-oxopentanoic  
acid (238e), was prepared from 237e by an analogous route to 235e which afforded a beige foam (190mg, 60%): [α]<sub>D</sub><sup>20</sup> -78 (c 0.145, MeOH); IR (KBr) 3400, 3070, 2955, 2925, 2855, 1653, 1576, 1541, 1490, 1445, 1427, 1342, 1280, 1258, 1205, 1189, 1137, 1075, 1023, 983, 930,

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878, 843, 801, 777, 722;  $^1\text{H}$  NMR ( $\text{D}_6$ -DMSO)  $\delta$  9.40 (1H, s), 8.72-8.60 (2H, m), 7.89 (2H, d), 7.56-7.44 (3H, m), 5.17 (1H, m), 4.90-4.83 (1H, m), 4.46-4.36 (1H, m), 4.20-4.15 (1H, m), 3.40-3.30 (1H, m), 2.98-2.90 (2H, m), 2.50-1.60 (10H, m).



(1S,9S) t-Butyl 9-benzoylamino-octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (243),  
 10 was prepared from (1S,9S) t-butyl 9-amino-octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate  
 (Attwood, et al. J. Chem. Soc., Perkin 1, pp. 1011-19 (1986)), by the method described for **211e**, to afford  
 2.03g (86%) of a colourless foam:  $[\alpha]_{\text{D}}^{25} -15.9^\circ$  (c  
 15 0.5,  $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3400, 2976, 2937, 1740, 1644, 1537, 1448, 1425, 1367, 1154;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.88-  
 7.82 (2H, m), 7.60-7.38 (4H, m), 5.48 (1H, m), 4.98  
 (1H, m), 3.45 (1H, m), 3.22-2.96 (2H, m), 2.64 (1H, m),  
 2.43-2.27 (2H, m), 1.95 (2H, m), 1.82-1.36 (4H, m),  
 20 1.50 (9H, s); Anal. Calcd for  $\text{C}_{21}\text{H}_{29}\text{N}_3\text{O}_4 \cdot 0.25\text{H}_2\text{O}$ : C,

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64.35; H, 7.59; N, 10.72. Found: C, 64.57; H, 7.43; N, 10.62. MS (ES +, m/z) 388 (100%,  $M^+ + 1$ ).

**(1S,9S) 9-Benzoylamino-octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid**

5 (244), was prepared from (1S,9S) t-butyl 9-benzoylamino-octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (243), by the method described for 212e, to afford 1.52g (89%) of a white powder: mp. 166-169 °C (dec);  $[\alpha]_D^{25}$  -56.4 ° (c

10 0.5, CH<sub>3</sub>OH); IR (KBr) 3361, 2963, 2851, 1737, 1663, 1620, 1534, 1195, 1179; <sup>1</sup>H NMR (D<sub>6</sub>-DMSO) δ 12.93 (1H, brs), 8.44 (1H, d, J = 8.4), 7.93 (2H, m), 7.54 (3H, m), 5.46 (1H, m), 4.87 (1H, m), 3.12 (2H, m), 2.64 (1H, m), 2.64 (1H, m), 2.27 (1H, m), 1.98-1.68 (7H, m), 1.40

15 (1H, m); Anal. Calcd for C<sub>17</sub>H<sub>21</sub>N<sub>3</sub>O<sub>4</sub> · 0.25H<sub>2</sub>O: C, 60.79; H, 6.45; N, 12.51. Found: C, 61.07; H, 6.35; N, 12.55. MS (ES+, m/z) 332 (58%,  $M^+ + 1$ ), 211 (100).

**[3S,2RS(1S,9S)] N-(2-Benzoyloxy-5-oxotetrahydrofuran-3-yl)-9-benzoylamino-octahydro-10-oxo-6H-**

20 pyridazino[1,2-a][1,2]diazepine-1-carboxamide (245), was prepared from (1S,9S) 9-benzoylamino-octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxylic acid (244), by the method described for 213e, to afford 601mg (76%) of a colourless foam: IR (KBr) 3401, 2945,

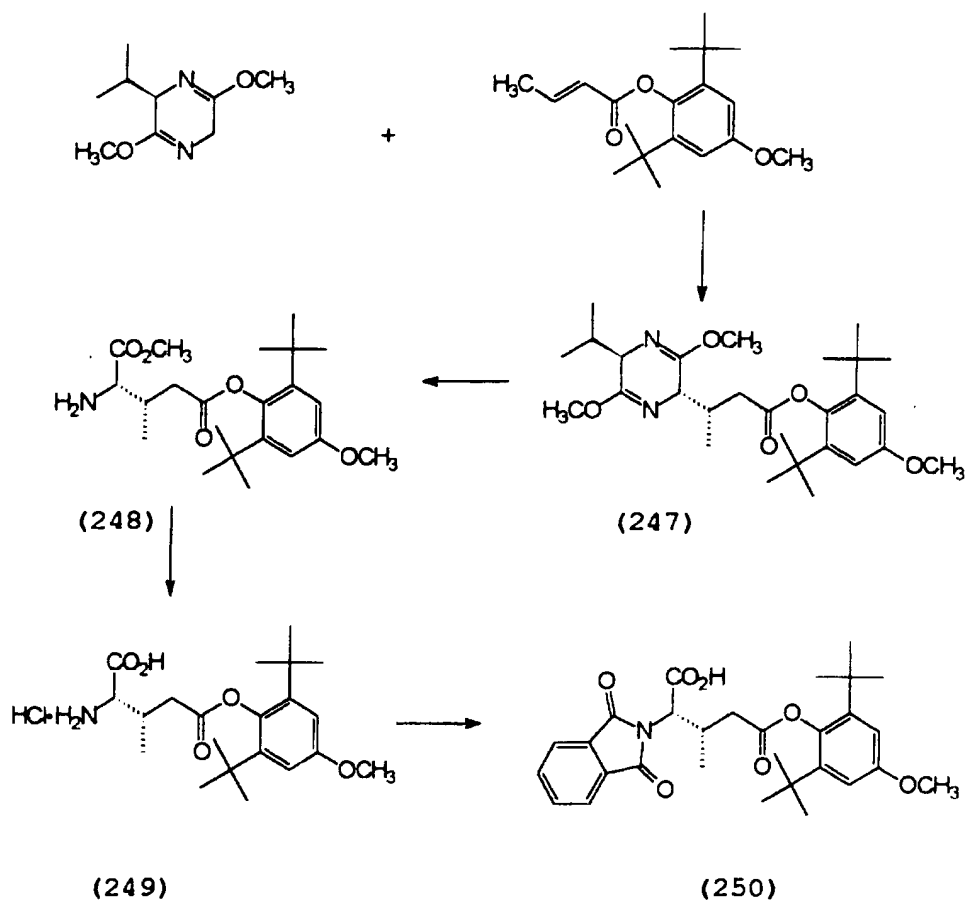
25 1794, 1685, 1638, 1521, 1451, 1120; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.87-7.77 (2H, m), 7.57-7.14 (10H, m), 5.59-5.47 (2H, m), 4.97-4.32 (4H, m), 3.27-1.35 (14H, m); Anal. Calcd for C<sub>28</sub>H<sub>32</sub>N<sub>4</sub>O<sub>6</sub> · 0.5H<sub>2</sub>O: C, 63.50; H, 6.28; N, 10.58. Found: C, 63.48; H, 6.14; N, 10.52. MS (ES +, m/z)

30 521 (100%,  $M^+ + 1$ ).

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[3*S*(1*S*,9*S*)] 3-(9-Benzoylamino-octahydro-10-oxo-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide-4-oxobutanoic acid (246), was prepared from [3*S*, 2*RS*(1*S*,9*S*)]N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-9-benzoylamino-octahydro-10-oxo-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide (245), by the method described for 214e, to afford 396mg (84%) of a white powder: mp. 110-115 °C;  $[\alpha]_D^{26}$  -126.3 ° (c 0.2, CH<sub>3</sub>OH); IR (KBr) 3345, 2943, 1787, 1730, 1635, 1578, 1528, 1488, 1450, 1429; <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.88 (2H, m), 7.48 (3H, m), 5.55 (1H, m), 4.91 (1H, m), 4.56 (1H, m), 4.29 (1H, m), 3.41-3.05 (3H, m), 2.76-2.41 (3H, m), 2.28-2.01 (3H, m), 1.86-1.65 (4H, m), 1.36 (1H, m); Anal. Calcd for C<sub>21</sub>H<sub>26</sub>N<sub>4</sub>O<sub>6</sub> · 1.25H<sub>2</sub>O: C, 55.68; H, 6.34; N, 12.37. Found: C, 55.68; H, 6.14; N, 12.16. MS (ES -, m/z) 429 (100%, M<sup>+</sup> - 1).

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[(3*S*(2*R*, 5*S*))-2,6-Di-tert-butyl-4-methoxyphenyl-3-[5-(2,5-dihydro-3,6-dimethoxy-2-(1-

- 5 **methylethyl)pyrazinyl)]butanoate (247)**. *n*-Butyllithium (1.6M in hexane) (22.3ml, 35.7mmol) was added dropwise over 20min to a solution of (2*R*)-(-)-2,5-dihydro-3,6-dimethoxy-2-(1-methylethyl)pyrazine (5.8ml, 6.0g, 32.4mmol) in THF (250ml) cooled to -75 °C at a rate  
 10 such that the temperature was maintained below -72 °C. The reaction mixture was stirred for 1h at -75 °C and a solution of 2,6-di-*t*-butyl-4-methoxyphenyl-2-butenate (Suzuck et al. Liebigs Ann. Chem. pp. 51-61 (1992))



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(9.9g, 32.5mmol) in THF (60ml) was added over 30 minutes maintaining the temperature below -72 °C during the addition. The reaction mixture was kept at -75 °C for 1.5h and a solution of glacial acetic acid (6ml) in THF (25ml) was added at -75 °C and the solution warmed to room temperature. The solution was poured onto 10% NH<sub>4</sub>Cl (300ml) and extracted with diethyl ether (3 x 250ml). The combined organic phases were washed with brine (2 x 200ml), dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness under reduced pressure. The residual oil was purified by flash chromatography on silica gel (20% heptane in CH<sub>2</sub>Cl<sub>2</sub>) which afforded the title compound as a light yellow oil (13.5g, 85%):  $[\alpha]_D^{20}$  -64 ° (c 0.22, MeOH); IR (KBr) 2962, 2873, 2840, 1757, 1697, 1593, 1460, 1433, 1366, 1306, 1269, 1236, 1187, 1157, 1126, 1063, 1038, 1011, 970, 924, 892, 867, 846, 831, 797, 773, 754; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 6.85 (2H, s), 4.21 (1H, t, J = 3.5), 3.98 (1H, t, J = 3.5), 3.79 (3H, s), 3.71 (3H, s), 3.69 (3H, s), 3.15 (1H, dd, J 17.8, 7.9), 2.86-2.81 (1H, m), 2.58 (1H, dd, J = 17.8, 5.9), 2.28-2.19 (1H, m), 1.33 (18H, s), 1.02 (3H, d, J = 6.8), 0.70 (6H, dd, J = 13, 6.8).

**(2S,3S)-5-[2,6-Di-t-butyl-4-methoxyphenyl]1-methyl-3-methylglutamate (248).** A solution of [3S(2R, 5S)]-2,6-di-t-butyl-4-methoxyphenyl-3-[5-(2,5-dihydro-3,6-dimethoxy-2-(1-methylethyl)pyrazinyl)]butanoate (247) (22.4g, 45.8mmol) in acetonitrile (300ml) and 0.25N HCl (366ml, 2 equiv) was stirred at room temperature under nitrogen atmosphere for 4 days. The acetonitrile was evaporated under reduced pressure and diethylether (250ml) was added to the aq. phase. The pH of the aq. phase was adjusted to pH8-9 with concentrated ammonia

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solution (32%) and the phases separated. The aq. phase was extracted with diethylether (2 x 250ml). The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to dryness under reduced pressure. The

5 residual oil was purified by flash chromatography on silica gel (2% methanol in CH<sub>2</sub>Cl<sub>2</sub>) which afforded the required product as a light yellow oil (8.2g, 45%):

[α]<sub>D</sub><sup>20</sup> +20 ° (c 0.26, MeOH); IR(KBr) 3394, 3332, 3000, 2962, 2915, 2877, 2838, 1738, 1697, 1593, 1453, 1430, 10

1419, 1398, 1367, 1304, 1273, 1251, 1221, 1203, 1183, 1126, 1063, 1025, 996, 932, 891, 866, 847, 800, 772, 745; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 6.85 (2H, s), 3.79 (3H, s), 3.74 (3H, s), 3.72-3.69 (1H, m), 3.05-2.85 (1H, m), 2.67-2.50 (2H, m), 1.32 (18H, s), 0.93 (3H, d, J = 7); Anal.

15 Calcd for C<sub>22</sub>H<sub>35</sub>NO<sub>5</sub>: C, 67.15; H, 8.96; N, 3.56. Found: C, 67.20; H, 9.20; N, 3.70.

**(2S,3S)-5-[2,6-Di-t-butyl-4-methoxyphenyl]3-methylglutamate (249).** A solution of (2S,3S)-5-[2,6-di-t-butyl-4-methoxyphenyl]3-methylglutamate (248)

20 (8.0g, 20.3mmol) in 5N HCl (200ml) was heated at reflux for 2h. The reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in cyclohexane (x4) and evaporated to dryness (x4) which afforded a white solid (7.9g, 93%): mp 230 °C; [α]<sub>D</sub><sup>20</sup>

25 +22 ° (c 0.27, MeOH); IR (KBr) 3423, 2964, 1755, 1593, 1514, 1456, 1421, 1371, 1303, 1259, 1201, 1179, 1138, 1106, 1060, 966, 926, 861, 790, 710; <sup>1</sup>H NMR (MeOD) δ 6.76 (2H, s), 4.02 (1H, d, J = 3.7), 3.67 (3H, s), 3.05-2.85 (1H, m), 2.80-2.55 (2H, m), 1.22 (18H, s),

30 1.09 (3H, d, J = 6.3); <sup>13</sup>C NMR (MeOD) δ 174.5, 171.4, 158.6, 145.2, 143.1, 113.2, 58.3, 56.3, 39.8, 36.9,

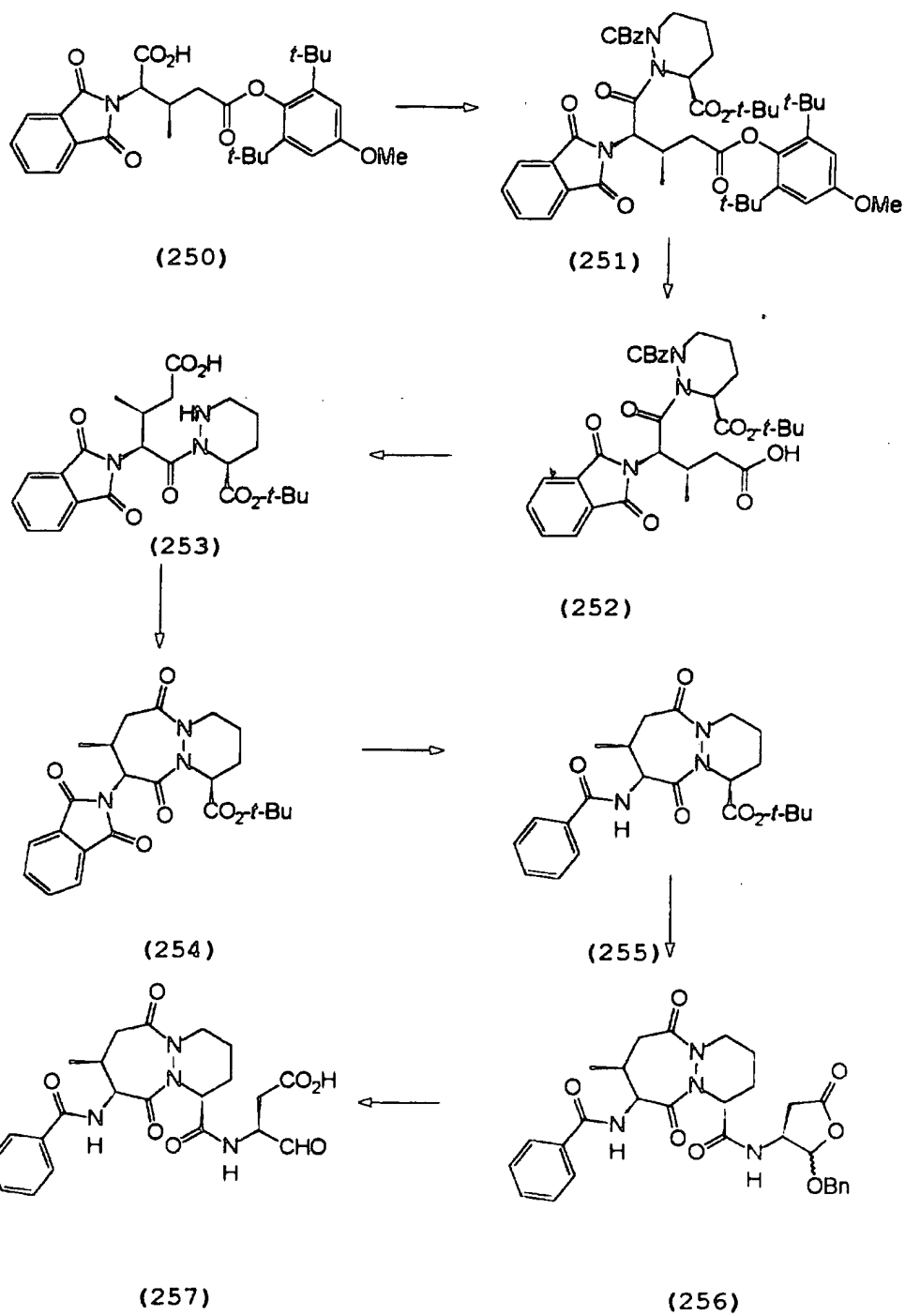
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32.5, 16.6; Anal. Calcd for  $C_{21}H_{34}ClNO_5$ : C, 60.64; H, 8.24; N, 3.37. Found: C, 60.80; H, 8.40; N, 3.40.

**(2S,3S)-5-[2,6-Di-t-butyl-4-methoxyphenyl]3-methyl-2-phthalimido-1,5-pentanedioate (250),**

- 5 Diisopropylethylamine (4.1ml, 3.04g, 23.5mmol, 1.25 equiv) and phthalic anhydride (3.5g, 23.6mmol, 1.25 equiv) were added to a solution of (2S,3S)-5-[2,6-di-t-butyl-4-methoxyphenyl]3-methylglutamate (249) (7.8g, 18.6mmol) in toluene (300ml). and the resulting mixture
- 10 was heated at reflux for 3 hours. After cooling to room temperature, the reaction mixture was evaporated to dryness and the resulting oil purified by flash chromatography on silica gel (2% methanol in  $CH_2Cl_2$ ) which afforded the required product as a white foam
- 15 (8.35g, 87%):  $[\alpha]_D^{20}$  -20 ° (c 1.04, MeOH); IR (KBr) 3480, 2968, 2880, 1753, 1721, 1594, 1462, 1422, 1388, 1303, 1263, 1216, 1183, 1148, 1062, 1003, 933, 899, 755, 723;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.92-7.87 (2H, m), 7.78-7.73 (2H, m), 6.84 (2H, s), 4.95 (1H, d), 3.78 (3H, s),
- 20 3.30-3.05 (2H, m), 2.85-2.65 (1H, m), 1.30 (18H, s), 1.13 (3H, d).

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1-(2,6-di-*t*-Butyl-4-methoxy)-phenyl-5-(1-benzyloxycarbonyl-3-*t*-butoxycarbonyl-hexahydro-pyridazin-2-yl)-3-methyl-4-phthalimidopentan-1,5-dioate (251). A solution of the amino acid (250) (1.2g, 2.35mmol) in dry diethylether (10ml) was treated with phosphorus pentachloride (0.52g, 2.5mmol) at room temperature for 2h. The mixture was concentrated and treated several times with toluene and again evaporated to dryness. The resulting acid chloride was dissolved in dry THF (5ml) and CH<sub>2</sub>Cl<sub>2</sub> (5ml) and cooled to 0 °C. *t*-Butyl-1-(benzyloxycarbonyl)-hexahydro-3-pyridazine-carboxylate (0.753g, 2.35mmol, 1 equiv) and *N*-ethylmorpholine (3ml) were added to the solution. The reaction mixture was stirred for 30min at 0 °C and then overnight at room temperature. The mixture was evaporated and the resulting residue taken up with CH<sub>2</sub>Cl<sub>2</sub> (30ml). The solution was washed with 1M HCl, water, 10% NaHCO<sub>3</sub>, dried (MgSO<sub>4</sub>) and evaporated. The resulting white foam was purified on silica gel (0-2% methanol in CH<sub>2</sub>Cl<sub>2</sub>) which afforded the required compound 251 as a pale yellow glassy solid (740mg, 39%):  $[\alpha]_D^{20}$  -22 (c 0.42, MeOH); IR (KBr) 3441, 2966, 1725, 1693, 1386, 1255, 1221, 1186, 1154, 1123, 1063, 724; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.94-7.89 (4H, m), 7.56-7.28 (5H, m), 6.84 (2H, 2s), 5.29-5.20 (2H, AB), 4.91-4.81 (1H, m), 4.05-3.88 (1H, m), 3.78 (3H, s), 3.75-3.80 (1H, m), 3.28-2.95 (2H, m), 2.23-1.51 (6H, m), 1.45 (9H, s), 1.31 (9H, s), 1.28 (9H, s), 1.27 (3H, d).

(1*S*, 8*S*, 9*S*) *t*-Butyl 6,10-dioxo-8-methyl-1,2,3,4,7,8,9,10-octahydro-9-phthalimido-6H-pyridazino[1,2-*a*][1,2]diazepin-1-carboxylate (254). A solution of the protected acid (251) (715mg, 0.893mmol)

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in acetonitrile was treated with Cerium (IV) ammonium nitrate (1.8g, 3.3mmol, 3.7 equiv) in water (3ml) for 4h at room temperature. Mannitol (600mg, 3.3mmol, 3.7 equiv) was added and the mixture was stirred for 1h.

5 Diethylether (50ml) and water (30ml) were added to the mixture. After decantation, the aq. phase was extracted with diethylether (4 x 50ml). The combined organic phase was washed with water, dried ( $\text{MgSO}_4$ ) and concentrated. Chromatography on silica gel (10% methanol in  $\text{CH}_2\text{Cl}_2$ ) afforded 5-(1-benzyloxycarbonyl-3-t-butoxycarbonyl-hexahydropyridazin-2-yl)carbonyl-3-methyl-4-phthalimidopentanoic acid (**252**) (360mg, 64%):  $[\alpha]_D^{20}$  -49.2 (c 0.118, MeOH). This product was used without further purification (360mg, 0.609mmol), and

15 was hydrogenated in methanol (30ml) using 10% Pd/carbon (36mg) for 3h. The reaction mixture was filtered and the resulting solution concentrated to afford the amine (**253**) as a foam (270mg, 96%)  $[\alpha]_D^{20}$  -56.1 (c 0.18 MeOH). The amine (**253**) was dissolved in dry THF (10ml) and

20 phosphorous pentachloride (305mg, 1.47mmol, 2.5 equiv) was added. The mixture was then cooled to -5 °C and N-ethylmorpholine was added under nitrogen. The reaction mixture was stirred overnight at room temperature. The mixture was concentrated and the residue taken up with

25  $\text{CH}_2\text{Cl}_2$  (20ml), cold  $\text{H}_2\text{O}$  (20ml), 1M HCl (20ml). After decantation, the aq. phase was reextracted with  $\text{CH}_2\text{Cl}_2$  (2 x 20ml). The combined organic phase was washed with 10%  $\text{NaHCO}_3$  and water, dried ( $\text{MgSO}_4$ ) and concentrated. The resulting oil was purified on silica gel (1% methanol in  $\text{CH}_2\text{Cl}_2$ ) affording the bicyclic compound

30 (**254**) as a solid (65mg, 25%):  $[\alpha]_D^{20}$  -77 (c 0.208, MeOH); IR (KBr) 3471, 3434, 2975, 2928, 1767, 1723, 1443, 1389, 1284, 1243, 1151, 1112, 720;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )

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$\delta$  7.94-7.69 (4H, m), 5.34-5.27 (1H, m), 4.89-4.66 (2H, m), 3.94-3.64 (2H, m), 3.02-2.84 (1H, m), 2.34-2.19 (2H, m), 1.94-1.61 (3H, m), 1.47 (9H, s), 1.14 (3H, d);  
Anal. Calcd for  $C_{23}H_{27}N_3O_6$ : C, 62.57; H, 6.17; N, 9.52.  
5 Found: C, 62.60; H, 6.40; N, 9.10.

(1S, 8S, 9S) t-Butyl-9-benzoylamino-6,10-dioxo-8-methyl-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxylate (255). A solution of the bicyclic compound (254) (70mg, 0.16mmol) in  
10 ethanol was treated with hydrazine hydrate (0.02ml, 4mmol, 2.5 equiv). After 5h stirring at room temperature, the mixture was concentrated and the resulting residue taken up in toluene and reevaporated. The residue was treated with 2M acetic acid (2ml) for  
15 16h. The resulting precipitate was filtered and washed with 2M acetic acid (10ml). The filtrate was basified with solid  $NaHCO_3$  and then extracted with EtOAc. The organic solution was washed with water, dried ( $MgSO_4$ ) and concentrated. Purification by flash chromatography  
20 on silica gel (2% methanol in  $CH_2Cl_2$ ) afforded the free amine as a foam (50mg, 100%). The amine (50mg, 0.16mmol) was dissolved in dioxane (1ml) and water (0.25ml) and treated with  $NaHCO_3$  (0.034g, 0.04mmol) followed by benzoylchloride (0.047ml, 0.40mmol, 2.8  
25 equiv). The mixture was stirred overnight at room temperature, then diluted with EtOAc (15ml). The organic solution was washed with 10%  $NaHCO_3$  and sat. aq. NaCl, dried ( $MgSO_4$ ) and concentrated. Purification  
30 by flash chromatography on silica gel (2% methanol in  $CH_2Cl_2$ ) afforded the benzamide 255 as a foam (67mg, 100%):  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.89-7.39 (5H, m), 6.79 (1H, d), 5.32-5.20 (1H, m), 4.98-4.82 (1H, m), 4.75-4.64

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(1H, m), 3.84-3.65 (1H, m), 3.09-2.89 (1H, m), 2.45-2.18 (2H, m), 2.00-1.61 (4H, m), 1.48 (9H, s), 1.28 (3H, d).

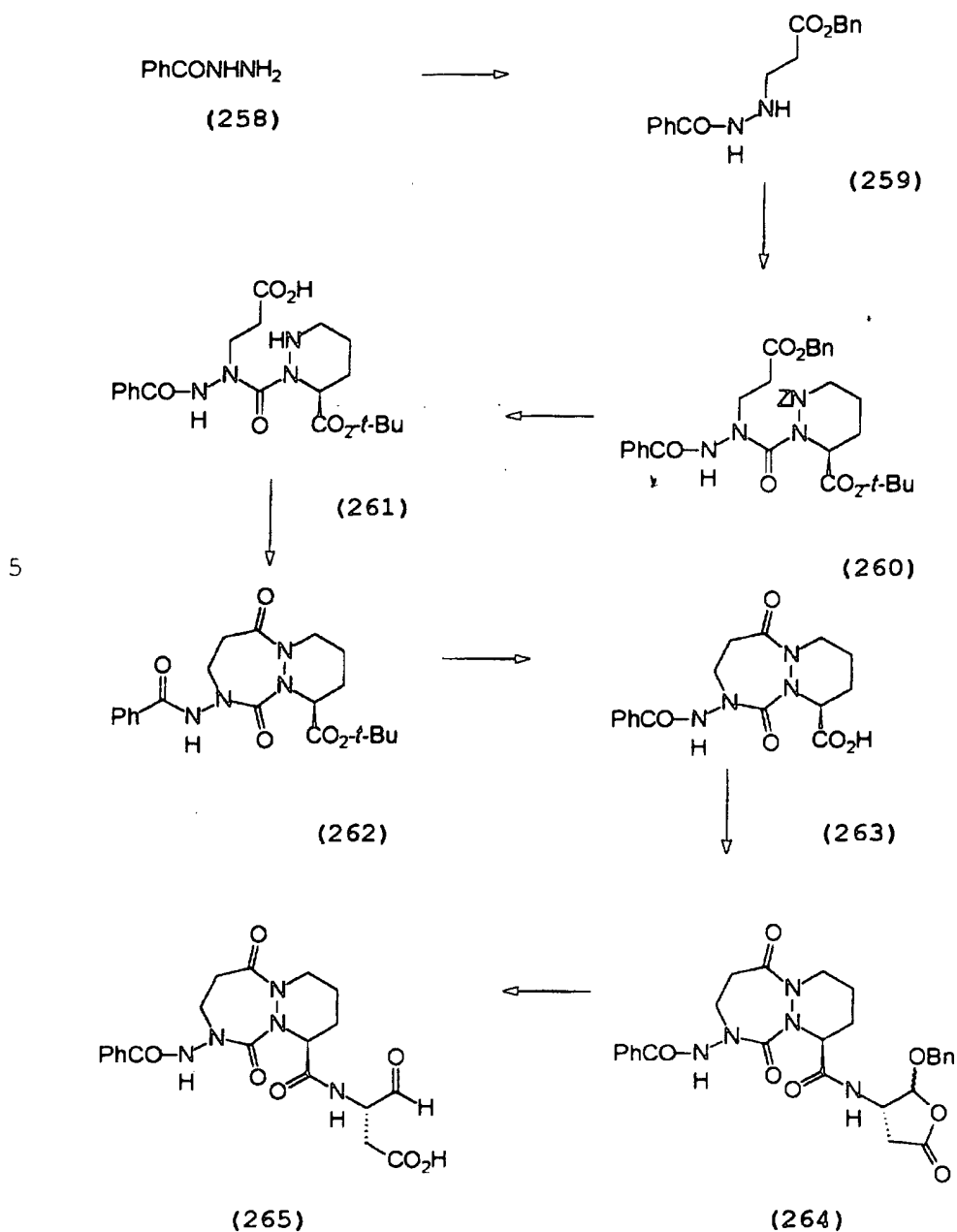
[3S(1S, 8S, 9S)] 3-(9-benzoylamino-6,10-dioxo-8-methyl-  
5 1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-  
[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid  
(257). A solution of t-butyl ester 255 (67mg, 0.16mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1ml) was treated at 0 °C with trifluoroacetic acid (1ml). The resulting solution was  
10 stirred at 0 °C for 15min and then at room temperature for 1h. The solution was concentrated, the residue taken up in dry CH<sub>2</sub>Cl<sub>2</sub> (2 x 2ml) and the mixture again concentrated (x2). The residue was crystallized from diethylether. Filtration of the precipitate afforded  
15 the free acid of 255 as a grey solid (40mg, 70%). A solution of acid (40mg, 0.11mmol), N-allyloxycarbonyl-4-amino-5-benzyloxy-2-oxotetrahydrofuran (Chapman, Bioorg. & Med. Chem. Lett., 2, pp. 615-18 (1992); 39mg, 0.13mmol, 1.2equiv) and (Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub> (3mg) in a mixture  
20 of dry CH<sub>2</sub>Cl<sub>2</sub> (1ml) and dry DMF (0.2ml) was treated dropwise with n-Bu<sub>3</sub>SnH (0.089ml, 0.33mmol, 3 equiv). The resulting solution was stirred at 25 °C for 10min and then 1-hydroxybenzotriazole (36mg, 0.266mmol, 2.4 equiv) was added. The mixture was cooled to 0 °C and  
25 ethyldimethylaminopropyl carbodiimide (31mg, 0.16mmol, 1.5equiv) was added. After stirring at 0 °C for 10min and then at room temperature overnight, the mixture was diluted with EtOAc (20ml) and the resulting solution washed successively with 1M HCl (2 x 5ml), 10% NaHCO<sub>3</sub>  
30 (2 x 5ml) and sat. aq. NaCl (5ml), dried (MgSO<sub>4</sub>) and concentrated. Flash chromatography on silica gel (2% methanol in CH<sub>2</sub>Cl<sub>2</sub>) afforded a mixture of



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diastereoisomers (256) as a grey solid (50mg, 82%). This product (256) was used without further purification (50mg, 0.091mmol) and was hydrogenated in methanol (5ml) using 10% Pd/carbon (30mg) for 24h. The  
5 reaction mixture was filtered and the resulting solution concentrated. Flash chromatography on silica gel (2-20% methanol in CH<sub>2</sub>Cl<sub>2</sub>) afforded compound 257 (9mg, 21%) as a white solid: <sup>1</sup>H NMR (D<sup>4</sup>-MeOH) δ 7.88-7.29 (5H, m), 5.18-4.99 (1H, m), 4.59-4.35 (3H, m),  
10 4.26-4.11 (1H, m), 3.65-3.41 (2H, m), 3.18-2.91 (1H, m), 2.62-1.47 (8H, m), 1.29-1.00 (3H, 2d) (mixture of acetal and hemiacetal). MS (ES -) 457.

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**Benzyl 3-(N'-benzoylhydrazino)propanoate (259).**

Benzylacrylate (1.13ml, 7.34mmol) was added to a stirred suspension of benzoylhydrazine (285) (1.0g, 7.34mmol) in isopropanol (28ml). The mixture was

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refluxed for 20h, cooled to room temperature then concentrated. The residue was purified by flash chromatography (20% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>) to afford **259** (1.098g, 50%) as an oil which crystallized on standing:

- 5 mp 65 °C; IR (KBr) 3283, 1723, 1644, 1316, 1201, 1156;  
<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.32-8.18 (1H, m), 7.81-7.70 (2H, m),  
7.57-7.23 (8H, m), 5.36-4.92 (1H, brm), 5.11 (2H, s),  
3.26 (2H, t, *J* = 6.5), 2.59 (2H, t, *J* = 6.5); <sup>13</sup>C NMR  
(CDCl<sub>3</sub>) δ 172.12, 167.27, 135.65, 132.54, 131.66,  
10 128.45, 128.10, 128.06, 126.84, 66.31, 47.33, 33.31;  
Anal. Calcd for C<sub>17</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>: C, 68.44; H, 6.08; N, 9.39.  
Found: C, 68.42; H, 6.10; N, 9.38. MS (ES +) 321 (M + Na, 38%), 299 (M<sup>+</sup> + 1, 100).

- (3S)-1-Benzyl 3-*t*-butyl 2-(N'-benzoyl-N-(2-  
15 benzyloxycarbonylethyl)hydrazinocarbonyl)hexahydro-  
pyridazine-1,3-dicarboxylate (**260**). A solution of  
(3S)-1-benzyl 3-*t*-butyl hexahydropyridazine-1,3-  
dicarboxylate (Hassall et al. J. Chem. Soc. Perkin 1,  
pp. 1451-1454 (1979)) (925.3mg, 2.89mmol) and  
20 diisopropylethylamine (0.70ml, 4.0mmol) in a 1.93M  
toluene solution of phosgene (17.96ml, 34.7mmol) was  
stirred at room temperature for 45min, then  
concentrated to leave a yellow solid. To this solid  
was added toluene (18ml), hydrazide (**259**) (861.6mg,  
25 2.89mmol) and diisopropylethylamine (0.70ml, 4.0mmol).  
The mixture was stirred at room temperature for 2.75h,  
then concentrated. The resulting residue was taken up  
in EtOAc, washed twice with 1M HCl, brine, then dried  
(MgSO<sub>4</sub>), filtered and concentrated to afford 2.15g of  
30 crude material. Flash chromatography (40% EtOAc in  
hexane) afforded 1.65g (89%) of the title compound as a  
white foam: mp 40 °C; [α]<sub>D</sub><sup>24</sup> -55.78 ° (c 0.40, CH<sub>2</sub>Cl<sub>2</sub>);

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IR (KBr) 3436, 2930, 1733, 1689, 1455, 1412, 1367, 1258, 1156, 697;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.54-8.23 (0.5H, m), 7.97-7.09 (15.5H), 5.16-4.80 (4H, m), 4.66-4.32 (1H, m), 4.24-3.55 (3.3H, m), 3.50-3.26 (0.4H, m), 3.19-2.49 (2.3H, m), 2.11-1.43 (6H, m), 1.32-1.05 (7H, m); Anal. Calcd for  $\text{C}_{35}\text{H}_{40}\text{N}_4\text{O}_8 \cdot 0.5\text{H}_2\text{O}$ : C, 64.31; H, 6.32; N, 8.57. Found: C, 64.18; H, 6.27; N, 8.56. MS (ES +) 662 ( $\text{M} + \text{Na}$ , 84%), 645 ( $\text{M}^+ + 1$ , 100), 384 (77).

(6S)-3-(N'-benzoyl-N-(6-t-butoxycarbonylhexahydro-  
10 hydroyridazine-1-carbonyl)hydrazino)propanoic acid  
(261). A solution of 260 (1.59g, 2.47mmol) in MeOH (142ml) was treated with 10% Palladium on carbon (230.0mg) and stirred under an atmosphere of  $\text{H}_2$  for 1.5h. The mixture was filtered and the solvent  
15 evaporated to afford 1.04g (100%) of a white foam. This was used in the next step without further purification: mp  $< 40^\circ\text{C}$ ;  $[\alpha]_{\text{D}}^{26} +1.6^\circ$  (c 0.26,  $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3422, 2977, 2986, 1728, 1677, 1486, 1445, 1396, 1369, 1309, 1228, 1155, 916, 716;  $^1\text{H}$  NMR  
20 ( $\text{CDCl}_3$ )  $\delta$  10.0-9.7 (1H, brm), 7.86 (2H, d,  $J = 7.5$ ), 7.62-7.38 (3H, m), 7.3-5.6 (2H, brm), 4.57 (1H, brd,  $J = 4.0$ ), 4.05-3.77 (2H, m), 3.00-2.82 (1H, m), 2.80-2.43 (3H, m), 2.20-2.03 (1H, m), 2.00-1.47 (1H, m), 1.62-1.14 (11H, m);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  175.00, 171.17, 167.62,  
25 160.68, 132.39, 131.77, 128.67, 127.38, 82.27, 54.38, 48.04, 46.35, 33.62, 28.02, 25.68, 21.61. MS (ES +) 443 ( $\text{M} + \text{Na}$ , 68%), 421 ( $\text{M}^+ + 1$ , 100), 365 (50), 131 (61).

(4S) t-Butyl 7-benzamido-6,10-dioxo-1,2,3,4,7,8,9,10-  
30 octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (262). To a solution of amino acid 261

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(1.012g, 2.41mmol) in dry THF (26ml) at 0 °C was added N-ethylmorpholine (597µl, 4.69mmol), followed by PCl<sub>5</sub> (651.3mg, 3.12mmol). The reaction was stirred at 0 °C for 2h, then allowed to warm to rt and stirred for a further 15.5h. The mixture was concentrated and the resulting residue taken up in EtOAc, washed twice with 1M HCl, sat. NaHCO<sub>3</sub>, brine, then dried (MgSO<sub>4</sub>), filtered and concentrated. Flash chromatography (20% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>) gave 727.3mg (75%) of the title compound as a white foam:  $[\alpha]_D^{26} +51.0^\circ$  (c 0.20, CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3436, 2979, 1733, 1670, 1483, 1437, 1420, 1299, 1243, 1156; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.70 (1H, s), 7.78 (2H, d, J = 7.0), 7.57-7.32 (3H, m), 5.08 (1H, dd, J = 2.5, 5.5), 4.59-4.43 (1H, m), 4.08-3.69 (3H, m), 3.07-2.84 (1H, m), 2.57-2.35 (1H, m), 2.34-2.14 (1H, m), 2.07-1.43 (3H, m), 1.48 (9H, s); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 172.41, 169.04, 166.35, 158.35, 132.24, 132.03, 128.61, 127.31, 82.77, 55.41, 54.07, 41.57, 32.21, 28.04, 24.97, 20.37; Anal. Calcd for C<sub>20</sub>H<sub>26</sub>N<sub>4</sub>O<sub>5</sub>: C, 59.69; H, 6.51; N, 13.92. Found: C, 59.53; H, 6.53; N, 13.84. MS (ES +) 425 (M + Na, 71%), 403 (M<sup>+</sup> + 1, 100), 145 (41).

**(4S)-7-Benzamido-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic Acid (263).** A solution of ester 262 (720.0mg, 1.80mmol) in a 1:1 mixture of CH<sub>2</sub>Cl<sub>2</sub> and TFA (150ml) was stirred for 1.3h under a dry atmosphere. The solution was then reduced *in vacuo*, taken up in Et<sub>2</sub>O and reduced again. This process was repeated six times to afford the crude product as an off-white solid. The product was purified by flash chromatography (5% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) to afford 520.0mg (83%) of the title compound as a white

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foam:  $[\alpha]_D^{25} +59.5^\circ$  (c 1.82,  $\text{CH}_2\text{Cl}_2$ ); IR (KBr) 3435, 3266, 2956, 1732, 1664, 1524, 1486, 1440, 1302;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  9.13 (1H, s), 7.77 (2H, d,  $J = 7.5$ ), 7.57-7.32 (3H, m), 5.27-5.16 (1H, m), 4.62-4.43 (1H, m), 4.09-2.70 (3H, m), 3.14-2.89 (1H, m), 2.59-2.43 (1H, m), 2.38-2.20 (1H, m), 2.14-1.89 (1H, m), 1.82-1.59 (2H, m);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  173.65, 172.28, 166.44, 158.42, 132.44, 131.31, 128.61, 127.39, 54.83, 54.01, 42.11, 31.79, 24.42, 20.29; MS (ES -) 345 (M -  $\text{H}^+$ , 100%), 161 (45).

**[2RS,3S(4S)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide (264).**

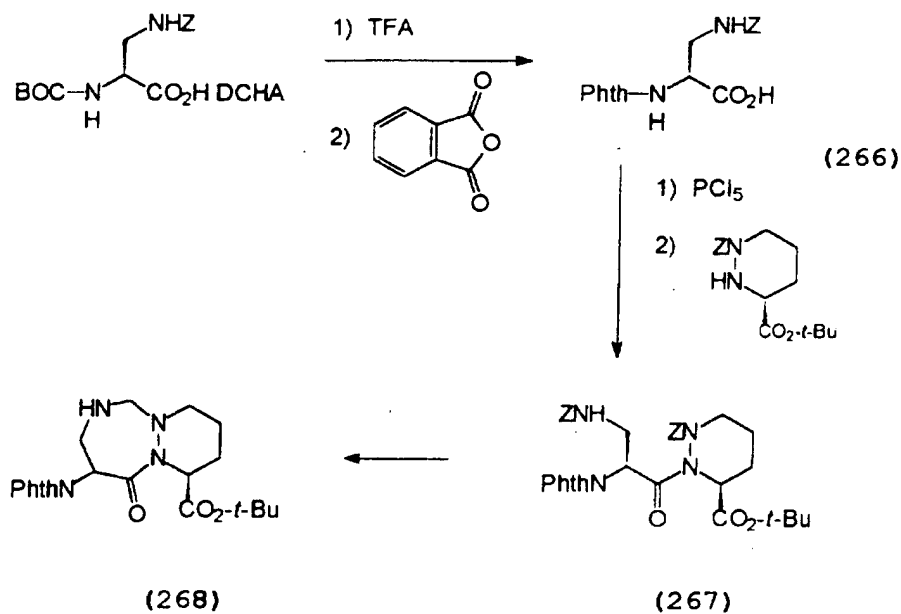
To a solution of acid 263 (300.0mg, 0.87mmol) and (2RS,3S)-3-allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydrofuran (Chapman, Bioorg. & Med. Chem. Lett. 2, pp. 615-18 (1992)) (277.6mg, 0.95mmol) in dry  $\text{CH}_2\text{Cl}_2$  (2.5ml) and dry DMF (2.5ml) at rt was added bis(triphenylphosphine) palladium chloride (13.0mg), followed by tri-n-butyltin hydride (466.0 $\mu\text{l}$ , 1.73mmol). The reaction was stirred for 5min, then 1-hydroxybenzotriazole (234.1mg, 1.73mmol) was added and the mixture was cooled to 0  $^\circ\text{C}$  before addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (204.5mg, 1.04mmol). The mixture was allowed to warm to rt and stirred for 16.5h. The mixture was diluted with EtOAc, washed with 1M  $\text{NaHSO}_4$  twice with sat.  $\text{NaHCO}_3$ , then  $\text{H}_2\text{O}$  and brine. The organic layer was dried ( $\text{MgSO}_4$ ), filtered and concentrated. The residue was purified by flash chromatography (5% MeOH in  $\text{CH}_2\text{Cl}_2$ ) to afford 358.3mg (77%) of the title compound as a white solid: IR (KBr) 3435, 1791, 1665, 1526,

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1421, 1285;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.76 and 8.49 (1H, 2 x s), 7.92-7.73 (2H, m), 7.62-7.24 (8.5H, m), 6.86 (0.5H, d,  $J = 8.0$ ), 5.53 and 5.33 (1H, d,  $J = 5.5$ , s), 4.95-4.34 (5H, m), 4.04-3.54 (3H, m), 3.03-2.64 (2H, m), 2.49-2.14 (2H, m), 2.11-1.46 (4H, m); MS (ES +) 558 ( $\text{M} + \text{Na}$ , 100%), 536 ( $\text{M}^+ + 1$ , 78), 404 (58).

[3S(4S)]3-(7-Benzamido-6,10-dioxo-1,2,3,4,7,8;9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido)-4-oxobutanoic acid (265). A mixture of  
10 264 (350.0mg, 0.65mmol), 10% palladium on carbon (350mg) and methanol (36ml) was stirred under an atmosphere of  $\text{H}_2$  for 6.5h. The mixture was filtered and the solvent evaporated.  $\text{Et}_2\text{O}$  was added and the solvent removed again. This process was repeated four  
15 times to reveal 283mg (97%) of the title compound, as a white crystalline solid: mp decarboxylates above  $140^\circ\text{C}$ ;  $[\alpha]_{\text{D}}^{26} +33.5^\circ$  (c 0.18, MeOH), IR (KBr) 3428, 1663, 1528, 1487, 1437, 1288;  $^1\text{H}$  NMR ( $\text{D}_6$ -DMSO)  $\delta$  10.56 (1H, s), 8.71-8.57 (1H, m), 7.88-7.81 (2H, m), 7.65-  
20 7.46 (3H, m), 4.97-4.85 (1H, m), 4.38-4.0 (3H, m), 3.88-3.52 (3H, m), 2.91-2.71 (2H, m), 2.50-2.38 (1H, m), 2.35-2.21 (1H, m), 2.10-1.94 (1H, m), 1.93-1.49 (3H, m);  $^{13}\text{C}$  NMR ( $\text{D}_6$ -DMSO)  $\delta$  173.66, 172.49, 169.97, 169.89, 164.96, 157.62, 132.35, 131.85, 128.39, 127.32,  
25 53.81, 52.69, 40.90, 33.17, 31.60, 24.40, 24.13, 19.24; MS (ES -).

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(2S) 3-Benzyloxycarbonylamino-2-phthalimidopropionic  
5 acid (266). A solution of (2S) 3-  
benzyloxycarbonylamino-2-tert-  
butoxycarbonylamino-2-phthalimidopropionic acid dicyclohexylamine  
salt (3g, 5.8mmol) in dichloromethane (200ml) was  
washed four times with 1M HCl solution, dried (MgSO<sub>4</sub>)  
10 and concentrated. The resulting oil was dissolved in  
dry dichloromethane (35ml), cooled to 0 °C and treated  
with trifluoroacetic acid (35ml). This solution was  
stirred at 0 °C for 1.5h then evaporated to dryness.  
Dichloromethane (50ml) was added to the residue then  
15 removed under vacuum. This process repeated six times  
to afford a white solid. The white solid was suspended  
in toluene (50ml), treated with powdered phthalic  
anhydride (940mg, 6.35mmol) and refluxed for 18h. The  
resulting solution was concentrated to afford an oil  
20 which was purified by flash chromatography (2-10%  
methanol/dichloromethane) to afford **266**, 2.01g (94%) as  
a white powder: IR (KBr) 3600-2500br, 1776, 1714,



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1530, 1469, 1455, 1392, 1263, 1131, 722;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.83 (2H, m), 7.72 (2H, m), 7.29 (5H, m), 5.41 (1H, m), 5.03 (2H, s), 3.90 (2H, m); MS (ES-), 367 (M - 1).

[3S (2S)] t-Butyl 1-benzyloxycarbonyl-2-(3-

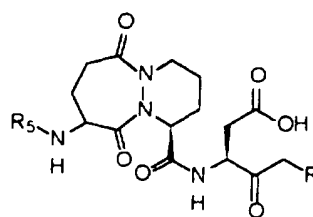
- 5 benzyloxycarbonylamino-2-phthalimidopropionyl)pyridazine-3-carboxylate (267). A suspension of the acid 266 (1.32g, 3.58mmol) in dry ether (37ml) was treated with phosphorus pentachloride (1.04g, 5mmol) and stirred at room temperature for 2h.
- 10 The solution was filtered to remove unreacted phosphorus pentachloride then evaporated to dryness. The residue was treated with dry toluene (25ml) then evaporated to dryness. This process was repeated several times. The resulting oil was dissolved in dry
- 15 dichloromethane (25ml), cooled to 0 °C and treated with a solution of (3S) t-butyl 1-benzyloxycarbonylpyridazine-3-carboxylate (1.15g, 3.58mmol) in dry dichloromethane (2ml) followed by 5% aqueous sodium bicarbonate solution (25ml). The
- 20 mixture was stirred rapidly at room temperature for 20h then diluted with ethyl acetate (100ml) and acidified to pH2 with 1M HCl. The organic phase was washed twice with dilute HCl solution then brine, dried ( $\text{MgSO}_4$ ) and concentrated. The resulting oil was purified by flash
- 25 chromatography (2-20% ethyl acetate/dichloromethane then 10-20% methanol/dichloromethane; to afford (267), 1.25g (52%) as a white powder: IR (KBr) 3367, 2955, 1722, 1517, 1455, 1387, 1369, 1251, 1153, 721;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.81 (2H, m), 7.74 (2H, m), 7.63 (1H, brs),
- 30 7.31 (10H, m), 5.46-4.76 (5H, m), 4.07-3.54 (4H, m), 2.4 (1H, m), 2.0-1.6 (3H, m), 1.40 (9H, s); MS (ES+), 671 (M + 1), 693 (M + Na).

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(1*S*,9*S*) *t*-Butyl 1,2,3,4,7,8,9,10-octahydro-10-oxo-9-phthalimido-6H-pyridazino[1,2-*a*][1,2,4]triazepine-1-carboxylate (**268**). A solution of ester **267** (50mg, 0.074mmol) in methanol (15ml) was treated with 10% palladium on carbon (50mg) and hydrogenated at room temperature and atmospheric pressure for 24h. The mixture was evacuated thoroughly to remove hydrogen then treated with 37% aqueous formaldehyde (18mg, 0.22mmol) and stirred under nitrogen for 2h. The mixture was filtered, evaporated to dryness and the product purified by flash chromatography (4-100% ethyl acetate/dichloromethane) to afford **268** 14.5mg (48%) as an oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.85 (2H, m), 7.71 (2H, m), 5.78 (1H, dd, *J* = 10, 5), 4.99 (1H, dd, *J* = 6.1, 1.5), 4.07 (1H, d, *J* = 10.6), 3.49 (1H, dd, *J* = 14, 5), 3.39 (1H, d, *J* = 10.3), 3.24 (1H, dd, *J* = 14, 10.2), 3.17 (2H, m), 2.39 (1H, m), 1.84-1.46 (3H), 1.51 (9H, s); MS (ES+), 415 (*M* + 1), 437 (*M* + Na).

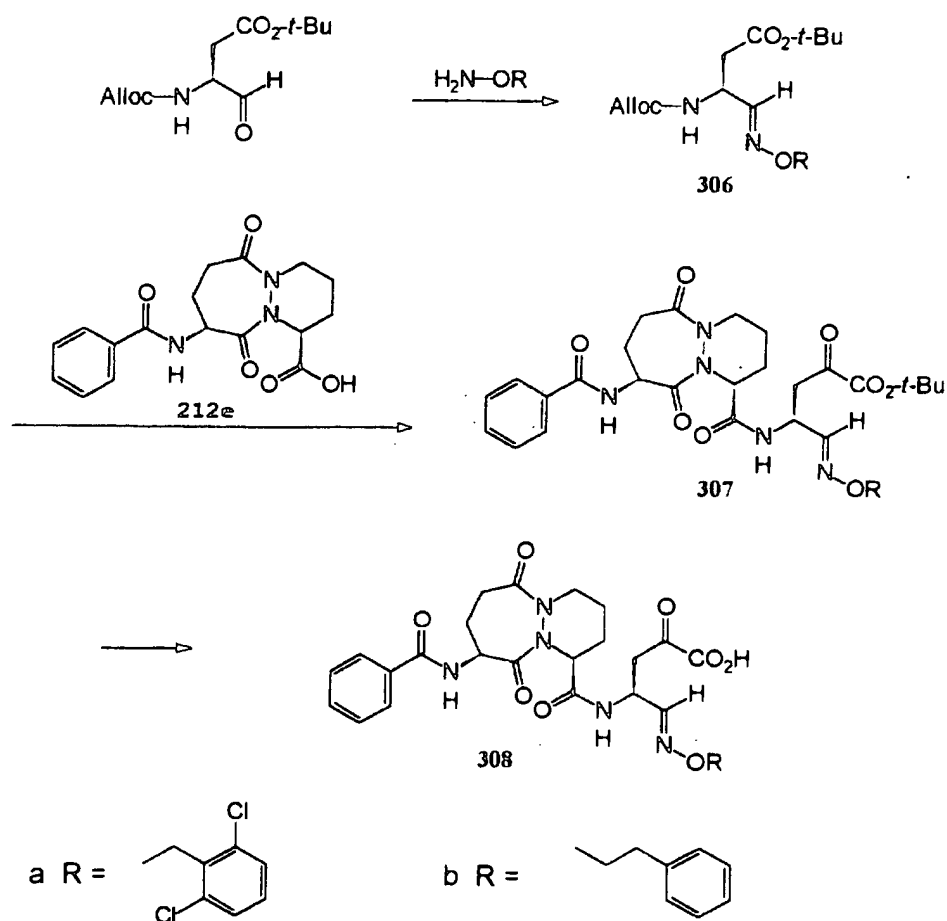
Compounds **280-283** were prepared from **212b** by a method similar to the method used to prepare **226e**. Compounds **284-287** were prepared by a method similar to the method used to prepare **217e**.

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**280-287**

compound	R <sub>5</sub>	R
280		
281		
282		
283		
284		
285		
286		
287		

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(3S) 3-Allyloxycarbonylamino-4-oxobutyric acid tert-butyl ester O-(2,6-dichlorophenylmethyl)oxime (306a) was prepared by a similar procedure as 208a except that 2,6-dichlorophenylmethoxyamine (prepared by a similar method as 306b) was used instead of semicarbazide to give 870mg (quant.) as a clear oil.

(3S) 3-Allyloxycarbonylamino-4-oxobutyric acid tert-butyl ester O-(2-(phenyl)ethyl)oxime (306b) was prepared by a similar procedure as 208a except that 2-

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(phenyl)ethoxyamine (US 5 346 911) was used instead of semicarbazide to give 395mg (quant.) as a clear oil.

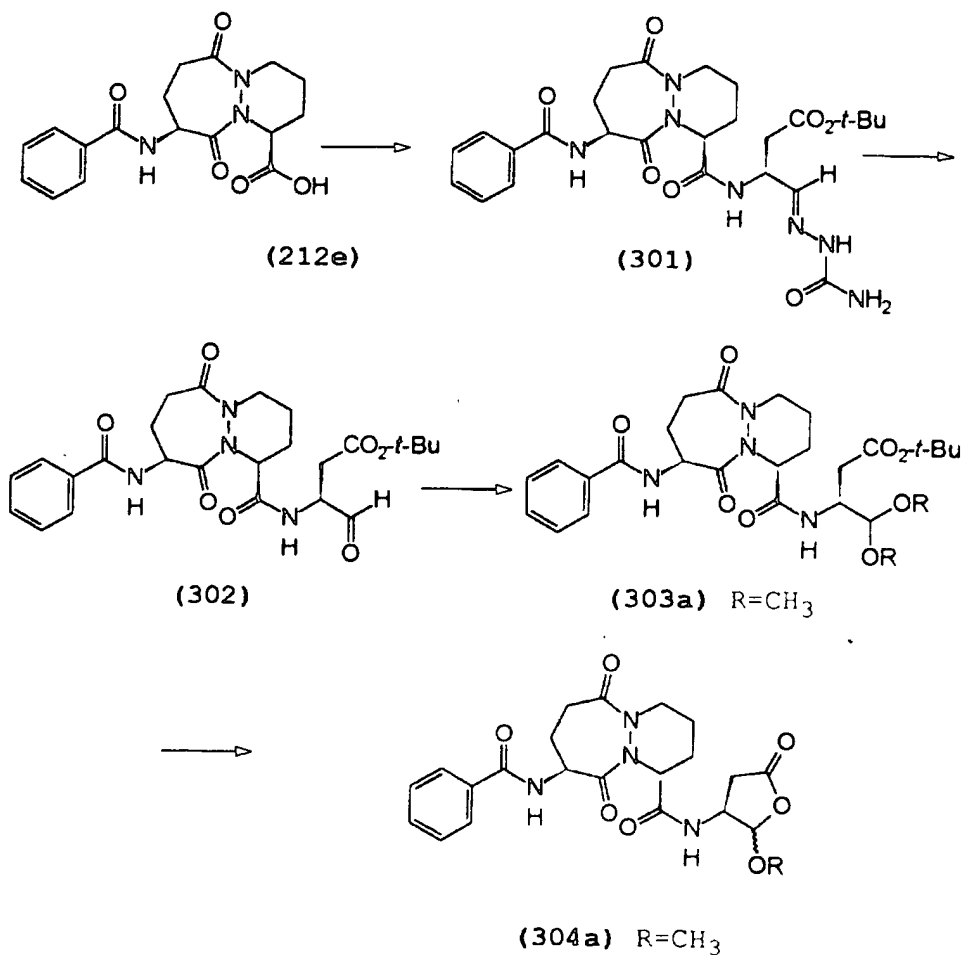
[3S(1S,9S) 3-(9-Benzoylamino-6,10-dioxo-  
1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-  
5 [1,2-a][1,2]diazapine-1-carboxamido)-amino]-4-  
oxobutanoic acid t-butyl ester, O-(2,6-  
dichlorophenylmethyl)oxime (307a) was prepared by a  
procedure similar to 233e except 306a was used instead  
of 207a to give 23 mg (23%) of 307a as a white solid.

10 [3S(1S,9S) 3-(9-Benzoylamino-6,10-dioxo-  
1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-  
[1,2-a][1,2]diazapine-1-carboxamido)-amino]-4-  
oxobutanoic acid t-butyl ester, O-(2-  
(phenyl)ethyl)oxime (307b) was prepared by a procedure  
15 similar to 233e except 306b was used instead of 207a to  
give 43 mg (48%) of 307b as a white solid.

[3S(1S,9S) 3-(9-Benzoylamino-6,10-dioxo-  
1,2,3,4,7,8,9,10-octahydro-6H-pyridazino-  
[1,2-a][1,2]diazapine-1-carboxamido)-amino]-4-  
20 oxobutanoic acid, O-(2,6-dichlorophenylmethyl)oxime  
(308a) was prepared by from 307a a procedure similar to  
the preparation of 235e from 234e to give 15.2 mg (74%)  
as white solid: <sup>1</sup>H NMR(CD<sub>3</sub>OD) δ 0.9(m), 1.3(s),  
1.7(m), 1.8(m), 2.0(m), 2.1-2.2(m), 2.3(dd), 2.4-  
25 2.5(m), 2.6(m), 2.7-2.8(m), 3.1(m), 3.3(m), 3.4-3.5(m),  
4.5(m), 4.9(m), 5.1(m), 5.3(d), 5.4(s), 6.8(d), 7.2-  
7.5(m), 7.8(dd), 8.4(dd).

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[3*S*(1*S*,9*S*) 3-(9-Benzoylamino-6,10-dioxo-  
 1,2,3,4,7,8,9,10-octahydro-6*H*-pyridazino-  
 [1,2-*a*][1,2]diazapine-1-carboxamido)-amino]-4-  
 oxobutanoic acid, *O*-(2-(phenyl)ethyl)oxime (308b) was  
 5 prepared by from 307b a procedure similar to the  
 preparation of 235e from 234e to give 25.2 mg (68%) as  
 white solid:  $^1\text{H}$  NMR(CD<sub>3</sub>OD)  $\delta$  1.2(m), 1.6-1.7(m), 2.0-  
 2.1(m), 2.2(m), 2.3(m), 2.5(m), 2.6-2.7(dd), 2.9(t),  
 3.0(t), 3.1(m), 3.3-3.5(m), 4.2(t), 4.25(m), 4.5(m),  
 10 5.2(t), 5.3(t), 6.7(d), 7.1-7.2(m), 7.35(dd), 7.4(m),  
 7.5(m), 7.8(dd), 8.3(dd).



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[3S(1S,9S) 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyriazino-[1,2-a][1,2]diazapine-1-carboxamido)-amino]-4-oxobutanoic acid tert-butyl ester (302).

5 **Step A:** 301 was prepared by procedure similar to 605a (Step A), except 212e was used instead of 603a to give 540 mg (34%) to give a white solid.

**Step B:** 302. A solution of 301 (50.7 mg; 0.091 mmol) in 2.8 ml of MeOH/HOAc/37% aq. formaldehyde (5:1:1) was  
10 stirred at rt for 5.5 h. and the reaction was concentrated to 0.7 ml *in vacuo*. The residue was dissolved in 3 ml of CH<sub>3</sub>CN and concentrated to 0.7 ml (3x), dissolved in toluene and concentrated to 0.7 ml *in vacuo* (2x), and concentrated to dryness.

15 Chromatography (flash, SiO<sub>2</sub>, 5% isopropanol/CH<sub>2</sub>Cl<sub>2</sub>) gave 302 (45.5 mg, 78%) as a white solid: <sup>1</sup>H NMR(DMSO-d<sub>6</sub>) δ 1.0-1.15(m, 2H), 1.4(s, 9H), 1.65(m, 2H), 1.9-2.1(m, 2H), 2.15-2.4(m, 3H), 2.55(m, 1H), 2.7-3.0(m, 2H), 4.3-4.6(m, 2H), 4.9(m, 1H), 5.2(m, 1H), 7.4-7.6(m, 2H),  
20 7.8-8.0(m, 2H), 8.6(m, 1H), 8.8(m, 1H), 9.4(s, 1H).

[1S,9S (2RS,3S)] 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-methoxy-5-oxo-tetrahydro-furan-3-yl)-6H-pyridazino[1,2-a][1,2]diazapine-1-carboxamide. (304a).

25 **Step A:** A solution of 302 (90 mg; 0.18 mmol) in 10 ml of MeOH was treated with trimethylorthoformate (1ml) and p-toluene sulfonic acid hydrate (5 mg; 0.026 mmol) and the reaction was stirred for 20 h. The reaction was treated with 3 ml of aq. sat. NaHCO<sub>3</sub> and  
30 concentrated *in vacuo*. The residue was taken up in

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EtOAc and washed with dilute aq.  $\text{NaHCO}_3$ , dried over  $\text{MgSO}_4$  and concentrated *in vacuo* to give 80 mg of **303a**.

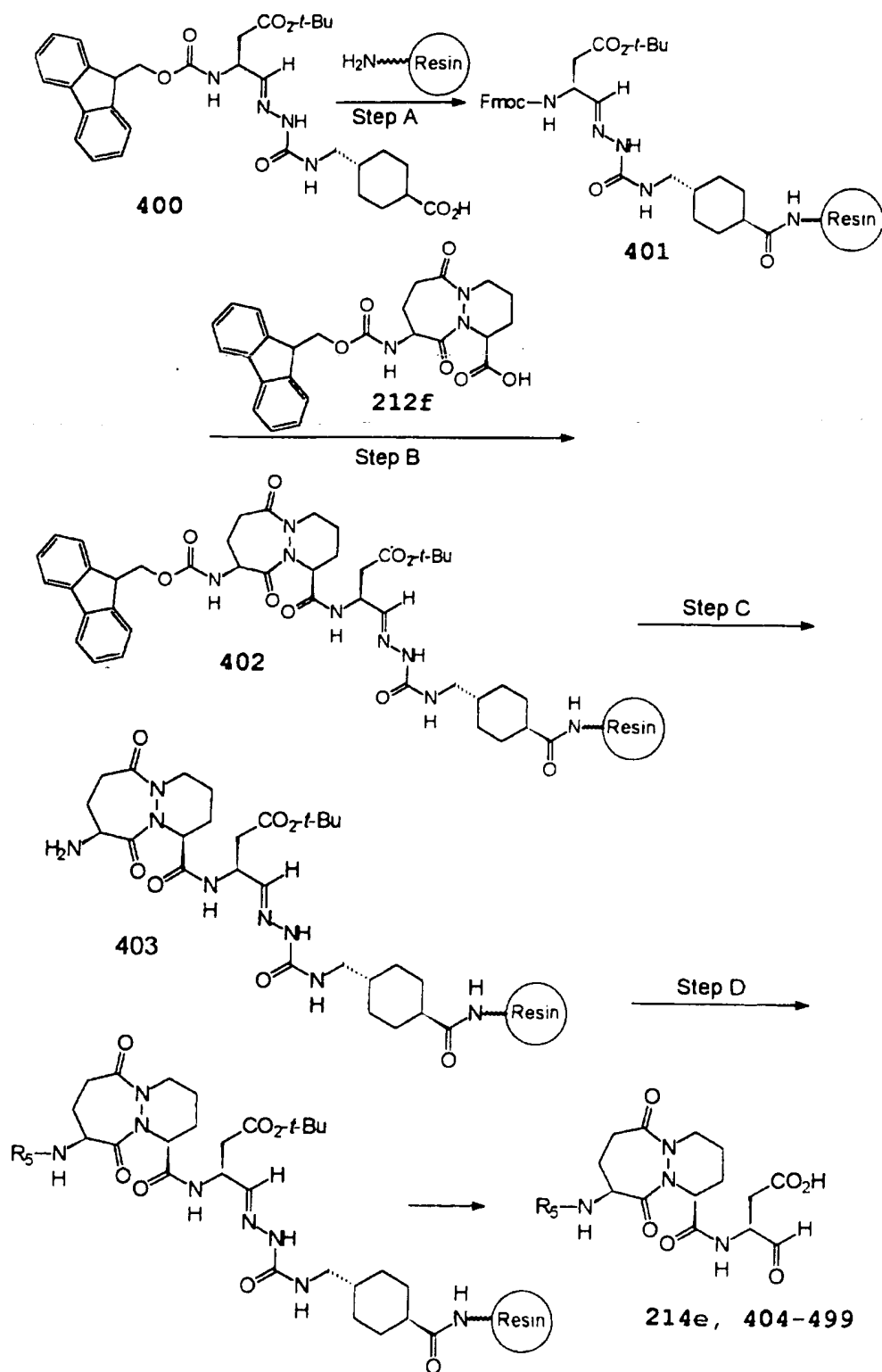
**Step B:** **303a** was dissolved in 2 ml of TFA and stirred at rt for 15 min. The reaction was dissolved in  $\text{CH}_2\text{Cl}_2$  and concentrated *in vacuo* (3x). Chromatography (flash,  $\text{SiO}_2$ , 1% to 3%  $\text{MeOH}/\text{CH}_2\text{Cl}_2$  gave 43 mg (64%) of **304a** as a white solid:  $^1\text{H}$  NMR( $\text{CDCl}_3$ )  $\delta$  1.55-1.8(m, 2H), 1.9-2.15(m, 4H), 2.25-2.5(m, 2H), 2.7-3.3(m, 4H), 3.45, 3.6(s, s, 3H), 4.4, 4.75(2m, 1H), 4.6(m, 1H), 4.95, 5.4(t,d, 1H), 5.1-5.2(m, 1H), 6.45, 7.05(2d, 1H), 6.95(m, 1H), 7.45(m, 2H), 7.5(m, 1H), 7.85(m, 2H).

#### Example 11

Compounds **214e**, **404-413**, **415-445**, **446-468**, **470-491**, and **493-499** were synthesized as described in Example 11 and Table 7.



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- Step A. Synthesis of 401.** TentaGel S<sup>®</sup> NH<sub>2</sub> resin (0.16 mmol/g, 10.0 g) was placed in a sintered glass funnel and washed with DMF (3 x 50 mL), 10% (v/v) DIEA in DMF (2 x 50 mL) and finally with DMF (4 x 50 mL).
- 5 Sufficient DMF was added to the resin to obtain a slurry followed by **400** (1.42 g, 2.4 mmol, prepared from (3S)-3-(fluorenylmethyloxycarbonyl)-4-oxobutryic acid t-butyl ester according to A.M. Murphy et. al. J. Am. Chem. Soc., 114, 3156-3157 (1992)), 1-
- 10 hydroxybenzotriazole hydrate (HOBt·H<sub>2</sub>O; 0.367 g, 2.4 mmol), O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU; 0.91 g, 2.4 mmol), and DIEA (0.55 mL, 3.2 mmol). The reaction mixture was agitated overnight at rt using a wrist arm shaker. The resin
- 15 was isolated on a sintered glass funnel by suction filtration and washed with DMF (3 x 50 mL). Unreacted amine groups were then capped by reacting the resin with 20% (v/v) Ac<sub>2</sub>O/DMF (2 x 25 mL) directly in the funnel (10 min/wash). The resin was washed with DMF (3
- 20 x 50 mL) and CH<sub>2</sub>Cl<sub>2</sub> (3 x 50 mL) prior to drying overnight in vacuo to yield **401** (11.0 g, quantitative yield).

- Step B. Synthesis of 402.** Resin **401** (6.0 g, 0.16 mmol/g, 0.96 mmol) was swelled in a sintered glass
- 25 funnel by washing with DMF (3 x 25 mL). The Fmoc protecting group was then cleaved with 25% (v/v) piperidine/DMF (25 mL) for 10 min (intermittent stirring) and then for 20 min with fresh piperidine reagent (25 mL). The resin was then washed with DMF (3
- 30 x 25 mL), followed by N-methylpyrrolidone (2 x 25 mL). After transferring the resin to a 100 mL flask, N-methylpyrrolidone was added to obtain a slurry followed

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by **212f** (0.725 g, 1.57 mmol), HOBT·H<sub>2</sub>O (0.25 g, 1.6 mmol), HBTU (0.61 g, 1.6 mmol) and DIEA (0.84 mL, 4.8 mmol). The reaction mixture was agitated overnight at rt using a wrist arm shaker. The resin work-up and  
5 capping with 20% (v/v) Ac<sub>2</sub>O in DMF were performed as described for **401** to yield **402** (6.21 g, quantitative yield).

**Step C. Synthesis of 403.** This compound was prepared from resin **402** (0.24 g, 0.038 mmol) using an  
10 Advanced ChemTech 396 Multiple Peptide synthesizer. The automated cycles consisted of a resin wash with DMF (3 x 1 mL), deprotection with 25% (v/v) piperidine in DMF (1 mL) for 3 min followed by fresh reagent (1 mL) for 10 min to yield resin **403**. The resin was washed  
15 with DMF (3 x 1 mL) and *N*-methypyrrolidone (3 x 1 mL).

**Step D. Method 1. [3S(1S,9S)]-3-(6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-9-(thiophene-3-carboxylamino)-6H-pyridazine[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (409).** Resin **403** was  
20 acylated with a solution of 0.4M thiophene-3-carboxylic acid and 0.4M HOBT in *N*-methypyrrolidone (1 mL), a solution of 0.4M HBTU in *N*-methypyrrolidone (0.5 mL) and a solution of 1.6M DIEA in *N*-methypyrrolidone (0.35 mL) and the reaction was shaken for 2 hr at rt. The  
25 acylation step was repeated. Finally, the resin was washed with DMF (3 x 1 mL), CH<sub>2</sub>Cl<sub>2</sub> (3 x 1 mL) and dried *in vacuo*. The aldehyde was cleaved from the resin and globally deprotected by treatment with 95% TFA/5% H<sub>2</sub>O (v/v, 1.5 mL) for 30 min at rt. After washing the  
30 resin with cleavage reagent (1 mL), the combined filtrates were added to cold 1:1 Et<sub>2</sub>O:pentane (12 mL)

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and the resulting precipitate was isolated by centrifugation and decantation. The resulting pellet was dissolved in 10% CH<sub>3</sub>CN/90% H<sub>2</sub>O/0.1% TFA (15 mL) and lyophilized to obtain crude **409** as a white powder. The  
5 compound was purified by semi-prep RP-HPLC with a Rainin Microsorb™ C18 column (5 μ, 21.4 x 250 mm) eluting with a linear CH<sub>3</sub>CN gradient (5% - 45%) containing 0.1% TFA (v/v) over 45 min at 12 mL/min. Fractions containing the desired product were pooled  
10 and lyophilized to provide **409** (10.8 mg, 63%).

**Step D. Method 1A. Synthesis of 418.** Following a similar procedure as method 1, resin **403** was acylated with 4-(1-fluorenylmethoxycarbonylamino)benzoic acid and repeated. The Fmoc group was removed as described  
15 in Step C and the free amine was acetylated with 20% (v/v) Ac<sub>2</sub>O in DMF (1 mL) and 1.6M DIEA in N-methylpyrrolidone (0.35 mL) for 2 hr at rt. The acetylation step was repeated. Cleavage of the aldehyde from the resin gave **418** (3.2 mg).

20 **Step D. Method 1B. Synthesis of 447.** Following a similar procedure as method 1A, resin **403** was acylated with 0.4M 4-(1-fluorenylmethoxycarbonylamino)benzoic acid. The acylation step was repeated once. The Fmoc group was  
25 removed as before and the free amine was reacted with 1M methanesulfonyl chloride in CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL) and 1M pyridine in CH<sub>2</sub>Cl<sub>2</sub> (0.60 mL) for 4 hr at rt. Cleavage of the aldehyde from the resin gave **447** (10.0 mg).

**Step D. Method 2. Synthesis of 214e.** Following  
30 a similar procedure as method 1, resin **403** was acylated

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with 0.5M benzoyl chloride in *N*-methypyrrolidone (1 mL) and 1.6M DIEA in *N*-methypyrrolidone (0.35 mL) for 2 hr at rt. The acylation step was repeated. Cleavage of the aldehyde from the resin gave **214e** (5.1 mg, 30%).

5       **Step D. Method 3. Synthesis of 427.** Following a similar procedure as method 1, resin **403** was reacted with 1.0M benzenesulfonyl chloride in CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL) and 1M pyridine in CH<sub>2</sub>Cl<sub>2</sub> (0.60 mL) for 4 hr at rt. The reaction was repeated. Cleavage of the aldehyde  
10 from the resin gave **427** (7.2 mg, 40%).

**Step D. Method 4. Synthesis of 420.** Following a similar procedure as method 1, resin **403** was reacted with 0.5M methylisocyanate in *N*-methypyrrolidone (1 mL) and 1.6M DIEA in *N*-methypyrrolidone (0.35 mL) for 2  
15 hr at rt. The reaction was repeated. Cleavage of the aldehyde from the resin gave **420** (8.3 mg, 55%).

**Step D. Method 5. Synthesis of 445.** Following a similar procedure at method 1, resin **403** was acylated with 0.27M imidazole-2-carboxylic acid (1 mL) in 2:1  
20 DMF:H<sub>2</sub>O (with 1 eq. DIEA) and 1M 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) in 2:1 *N*-methypyrrolidone/H<sub>2</sub>O (0.35 mL) for 3 hr at rt. Cleavage of the aldehyde from the resin gave **445** (9.5 mg).

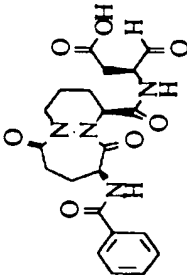
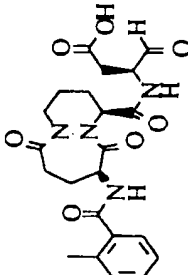
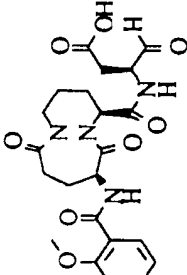
25 **Analytical HPLC methods:**

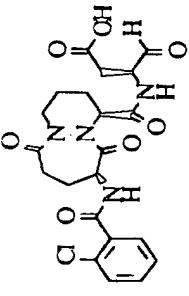
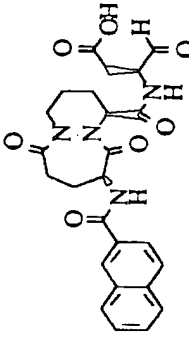
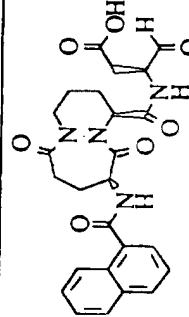
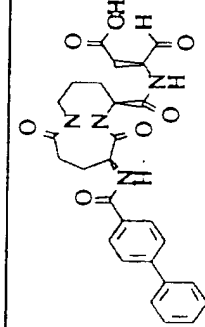
(1) Waters DeltaPak C18, 300A (5μ, 3.9 x 150 mm). Linear CH<sub>3</sub>CN gradient (5% - 45%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.

- 448 -

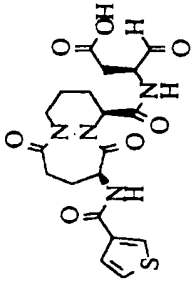
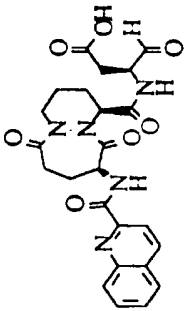
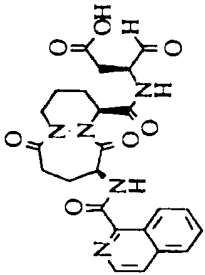
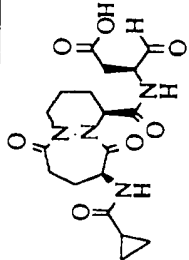
- (2) Waters DeltaPak C18, 300A (5 $\mu$ , 3.9 x 150 mm).  
Linear CH<sub>3</sub>CN gradient (0% - 25%) containing 0.1% TFA  
(v/v) over 14 min at 1 mL/min.
- (3) Waters DeltaPak C18, 300A (5 $\mu$ , 3.9 x 150 mm).  
5 Isocratic elution with 0.1% TFA/water (v/v) at 1  
mL/min.
- (4) Waters DeltaPak C18, 300A (5 $\mu$ , 3.9 x 150 mm).  
Linear CH<sub>3</sub>CN gradient (0% - 30%) containing 0.1% TFA  
(v/v) over 14 min at 1 mL/min.
- 10 (5) Waters DeltaPak C18, 300A (5 $\mu$ , 3.9 x 150 mm).  
Linear CH<sub>3</sub>CN gradient (0% - 35%) containing 0.1% TFA  
(v/v) over 14 min at 1 mL/min.

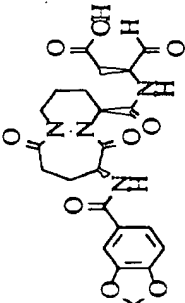
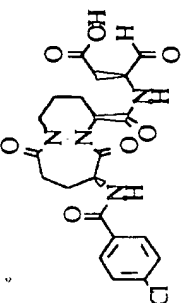
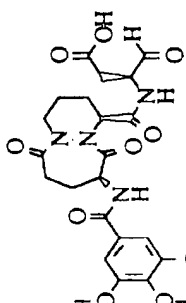
Table 7

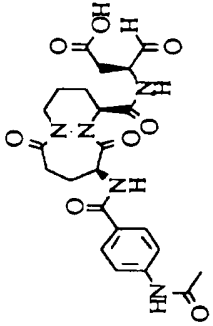
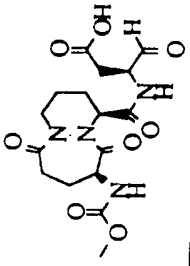
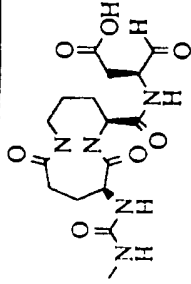
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
214e		C21H24N4O7	444.45	6.67 (2) 98%	445	2
404		C22H26N4O7	458.48	6.66 (2) 97%	459	2
405		C22H26N4O8	474.47	8.2 (1) 98%	475	2

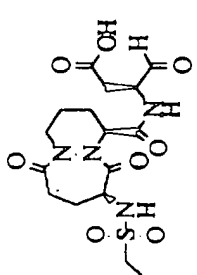
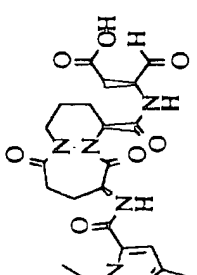
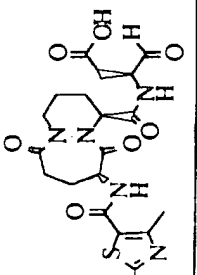
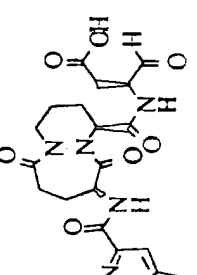
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) <sup>+</sup>	Syn. Method
406		C21H23ClN4O7	478.89	6.33 (1) 98%	479	2
407		C25H26N4O7	494.51	9.90 (1) 98%	495	2
408		C25H26N4O7	494.51	9.0 (1) 98%	495	2
409		C27H28N4O7	520.55	11.14 (1) 98%	521	2

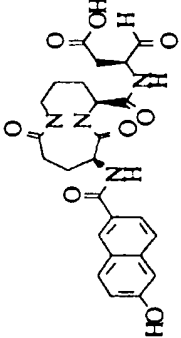
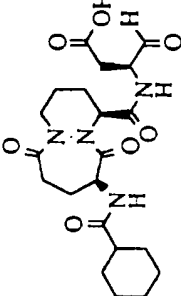
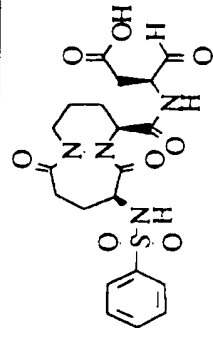


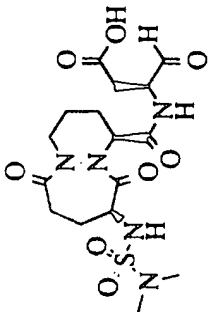
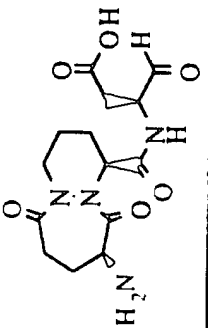
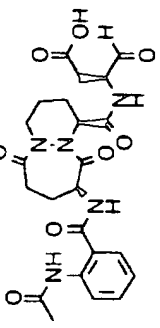
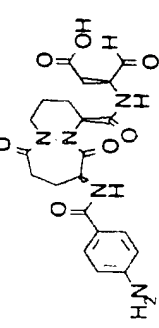
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410		C19H22N4O7S	450.47	4.87 (1) 98%	451	1
411		C24H25N5O7	495.50	10.7 (1) 98%	496	1
412		C24H25N5O7	495.50	8.57 (1) 98%	496	1
413		C18H24N4O7	408.41	7.21 (2) 98%	409	1

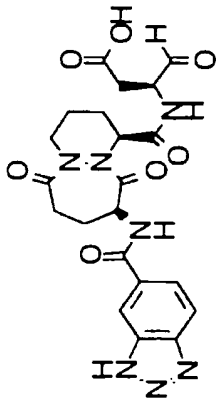
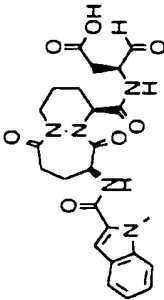
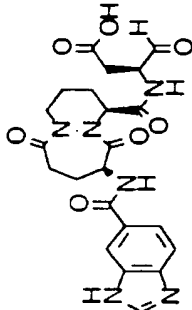
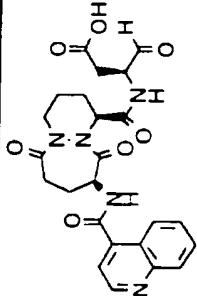
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415		C22H24N4O9	488.46	7.58 (1) 98%	489	1
416		C21H23ClN4O7	478.89	9.66 (1) 98%	479	1
417		C24H30N4O10	534.53	8.12 (1) 535	535	1

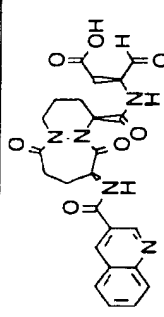
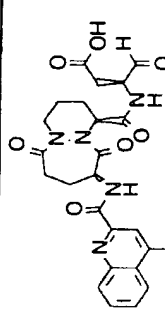
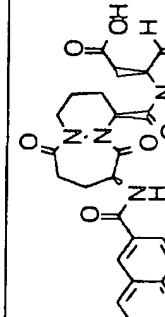
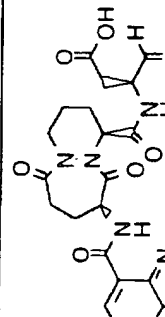
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
418		C23H27N5O8	501.50	5.93 (1) 98%	502	1A
419		C16H22N4O8	398.38	6.84 (2) 98%	399	2
420		C16H23N5O7	397.39	5.25 (2) 98%	398	4

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) <sup>+</sup>	Syn. Method
421		C16H24N4O8S	432.46	7.13 (2) 98%	433	3
422		C21H28N6O7	476.49	6.89 (1) 98%	477	1
423		C20H25N5O7S	479.52	5.62 (1) 98%	480	1
424		C19H23N5O8	449.42	6.28 (1) 450	450	1

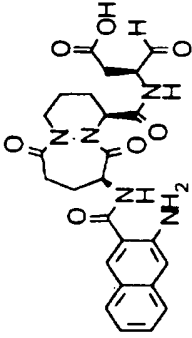
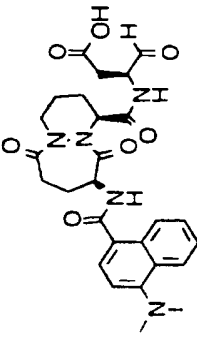
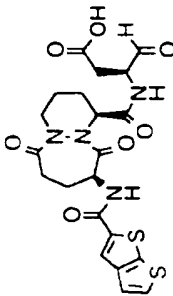
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) <sup>+</sup>	Syn. Method
425		C25H26N4O8	510.51	8.25 (1) 98%	511	1
426		C21H30N4O7	450.50	8.0 (1) 98%	451	2
427		C20H24N4O8S	480.50	7.87 (1) 98%	481	3

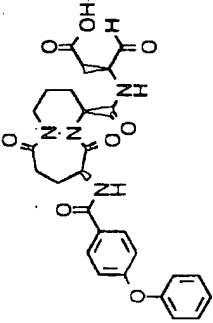
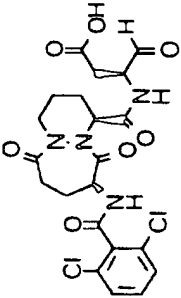
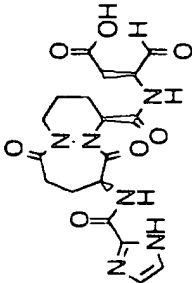
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) <sup>+</sup>	Syn. Method
428		C16H25N5O8S	447.47	5.13 (1) 98%	448	3
429		C14H20N4O6	340.34	3.19 (3) 98%	341	
430		C23H27N5O8	501.50	5.53 (1) 98%	502	1A
431		C21H25N5O7	459.46	6.66 (2) 98%	460	1

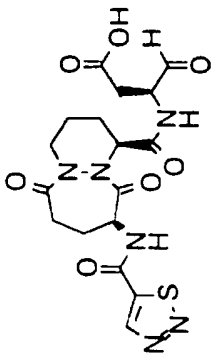
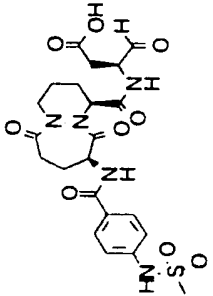
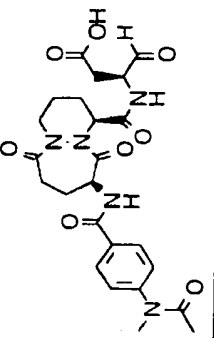
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) <sup>+</sup>	Syn. Method
432		C21H23N7O7	485.46	5.59 (1) 98%	486	1
433		C24H27N5O7	497.51	11.07 (1) 97%	498	1
434		C22H24N6O7	484.47	4.43 (1) 98%	485	1
435		C24H25N5O7	495.50	5.10 (1) 98%	496	1

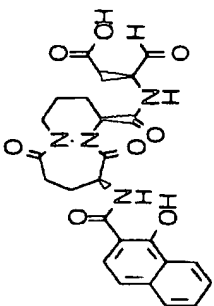
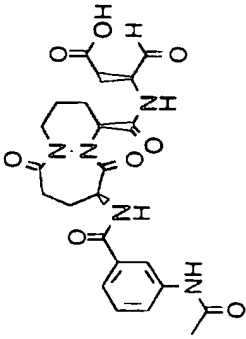
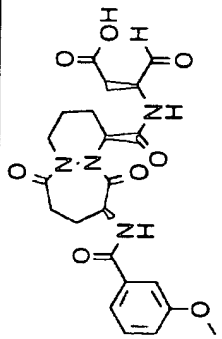
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) <sup>+</sup>	Syn. Method
436		C24H25N5O7	495.50	8.20 (4) 98%	496	1
437		C25H27N5O8	525.52	12.78 (5) 98%	526	1
438		C24H25N5O7	495.50	4.85 (1) 98%	496	1
439		C24H25N5O7	495.50	8.70 (5) 98%	496	1

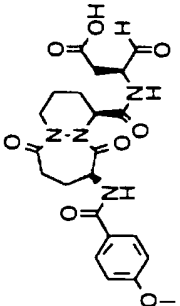
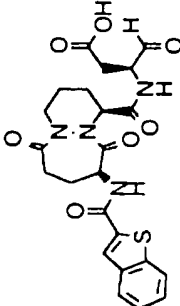
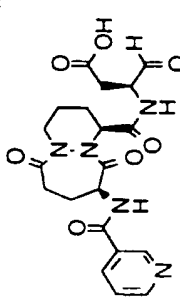
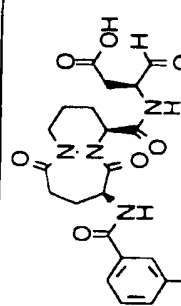


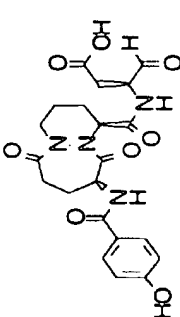
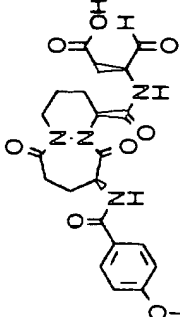
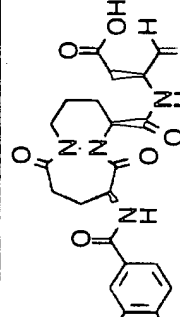
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
440		C25H27N5O7	509.52	9.96 (5) 98%	510	1
441		C27H31N5O7	537.58	6.15 (1) 98%	538	1
442		C21H22N4O7S2	506.56	10.10 (1) 98%	507	1

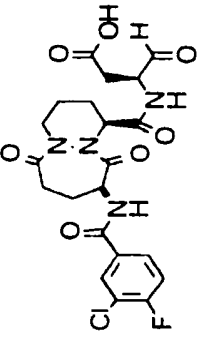
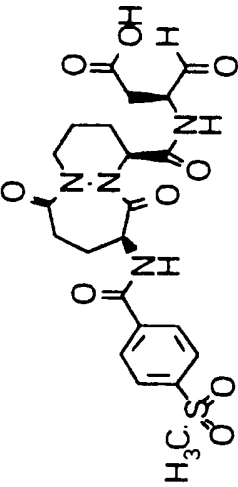
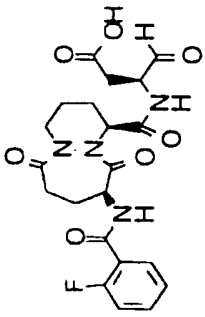
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
443		C27H28N4O8	536.55	13.12 (1) 98%	537	1
444		C21H22Cl2N4O7	513.34	9.96 (5) 98%	510	1
445		C18H22N6O7	434.41	5.72 (1) 98%	435	5

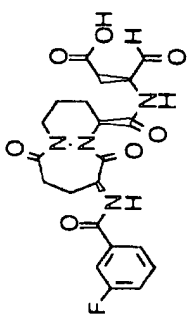
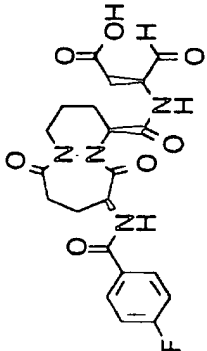
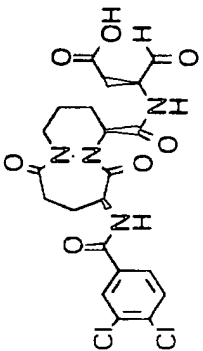
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
446		C17H20N6O7S	452.45	5.00 (1) 98%	453	1
447		C22H27N5O9S	537.55	6.32 (1) 98%	538	1B
448		C24H29N5O8	515.53	6.36 (1) 98%	516	1A

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) <sup>+</sup>	Syn. Method
449		C25H26N4O8	510.51	13.86 (1) 98%	511	1
450		C23H27N5O8	501.50	6.10 (1) 98%	502	1A
451		C22H26N4O8	474.47	8.02 (1) 98%	475	2

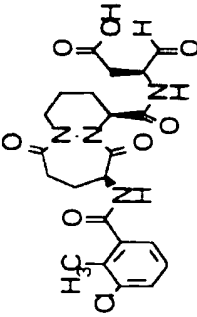
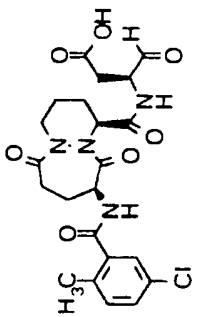
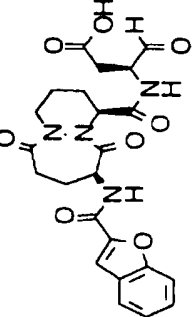
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
452		C22H26N4O8	474.47	7.77 (1) 98%	475	2
453		C23H24N4O7S	500.53	11.11 (1) 98%	501	2
454		C20H23N5O7	445.44	6.24 (2) 98%	446	2
455		C21H23ClN4O7	478.89	9.45 (1) 98%	479	2

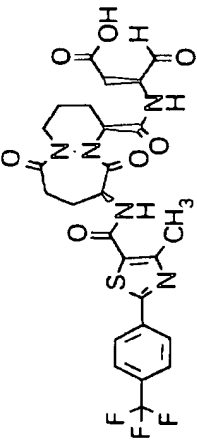
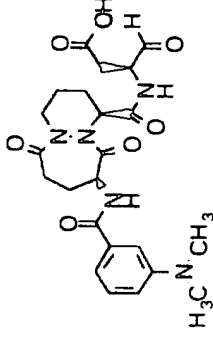
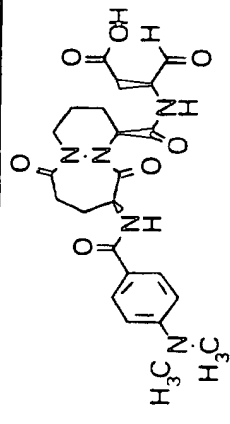
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) <sup>+</sup>	Syn. Method
456		C21H24N4O8	460.45	5.58 (1) 98%	(M+Na) 483	1
457		C28H28N4O10	580.56	10.42 (1) 98%	(M+Na) 603	1
458		C21H22F2N4O7	480.43	8.65 (1) 98%	481.1	1

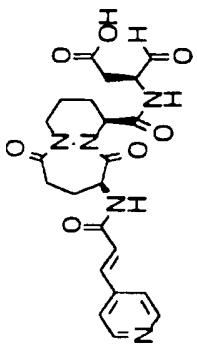
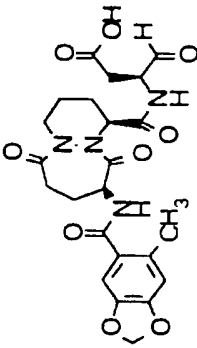
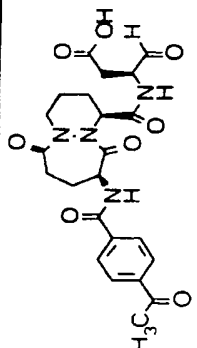
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) <sup>+</sup>	Syn. Method
459		C21H22ClFN4O7	496.88	10.11 (1) 98%	498.3	1
460		C22H26N4O9S	522.54	6.16 (1) 98%	523.6	1
461		C21H23FN4O7	462.44	7.41 (1) 98%	463.3	1

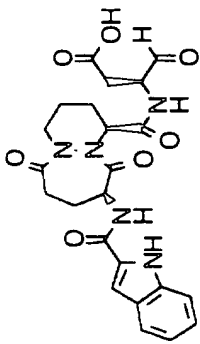
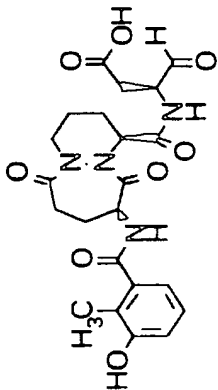
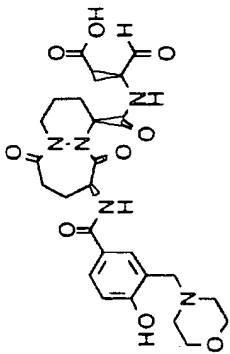
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) <sup>+</sup>	Syn. Method
462		C21H23FN4O7	462.44	7.71 (1) 98%	463.3	1
463		C21H23FN4O7	462.44	7.64 (1) 98%	464	1
464		C21H22Cl2N4O7	513.34	11.59 (1) 98%	414.5	1

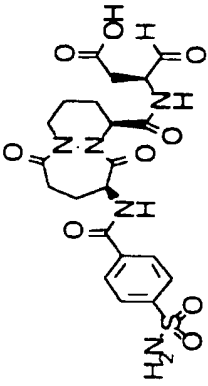
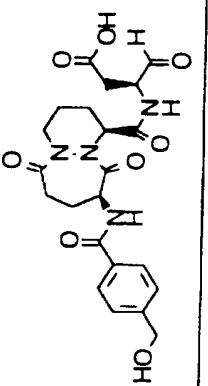
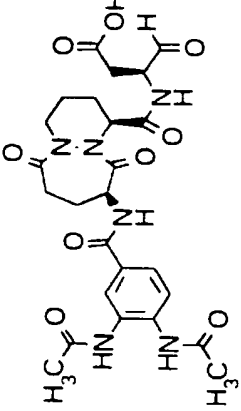


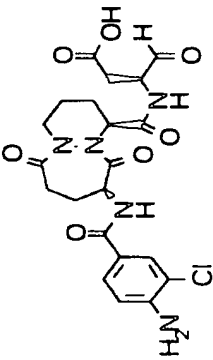
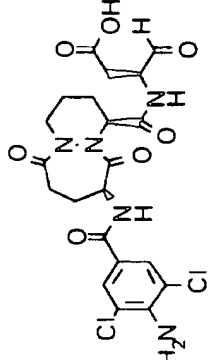
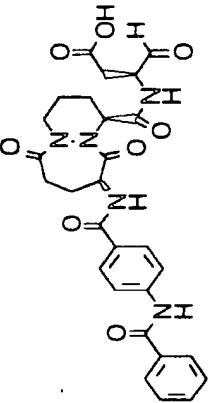
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
465		C22H25ClN4O7	492.92	9.65 (1) 98%	493.9	1
466		C22H25ClN4O7	492.92	9.63 (1) 98%	493.9	1
467		C23H24N4O8	484.47	9.73 (1) 98%	485.8	1

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) <sup>+</sup>	Syn. Method
468		C <sub>26</sub> H <sub>26</sub> F <sub>3</sub> N <sub>5</sub> O <sub>7</sub> S	609.59	14.84 (1) 98%	609.7	1
470		C <sub>23</sub> H <sub>29</sub> N <sub>5</sub> O <sub>7</sub>	487.52	4.57 (1) 98%	489.5	1
471		C <sub>23</sub> H <sub>29</sub> N <sub>5</sub> O <sub>7</sub>	487.52	5.74 (1) 98%	488.2	1

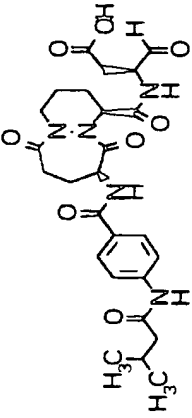
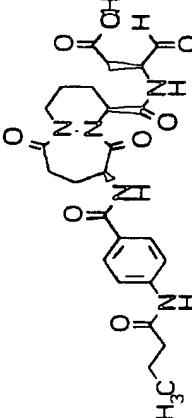
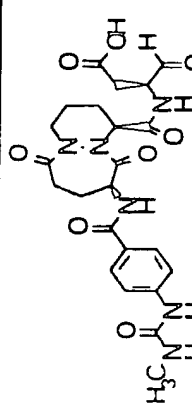
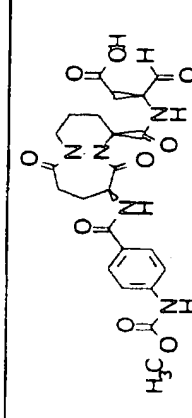
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
472		C22H25N5O7	471.47	4.00 (1) 98%	474	1
473		C23H26N4O9	502.49	7.65 (1) 98%	503.6	1
474		C23H26N4O8	486.49	7.16 (1) 98%	488.1	1

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) <sup>+</sup>	Syn. Method
475		C23H25N5O7	483.49	9.77 (1) 97%	485.1	1
476		C22H26N4O8	474.47	5.25 (1) 98%	475.8	1
477		C26H33N5O9	559.58	4.76 (1) 95%	561.8	1

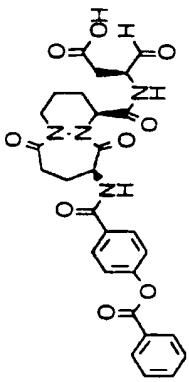
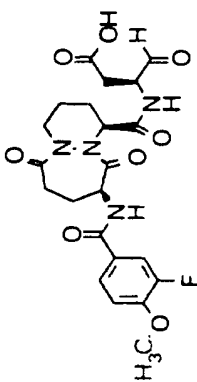
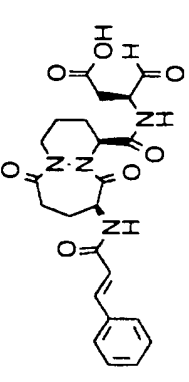
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
478		C21H25N5O9S	523.53	5.25 (1) 98%	524.3	1
479		C22H26N4O8	474.47	5.35 (1) 98%	475.8	1
480		C25H30N6O9	558.55	5.11 (1) 98%	559.3	1A

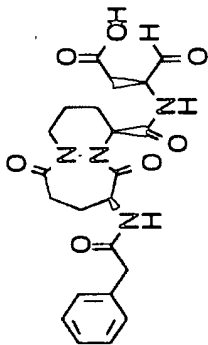
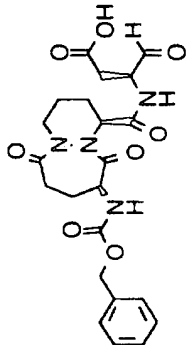
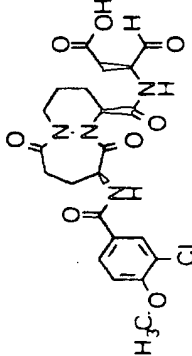
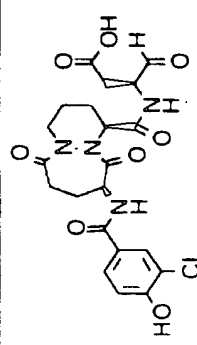
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
481		C <sub>21</sub> H <sub>24</sub> Cl <sub>2</sub> N <sub>5</sub> O <sub>7</sub>	493.9	7.10 (1) 98%	495.1	1
482		C <sub>21</sub> H <sub>23</sub> Cl <sub>2</sub> N <sub>5</sub> O <sub>7</sub>	528.4	9.05 (1) 98%	529.8	1
483		C <sub>28</sub> H <sub>29</sub> N <sub>5</sub> O <sub>8</sub>	563.57	10.01 (1) 98%	565.6	1,2

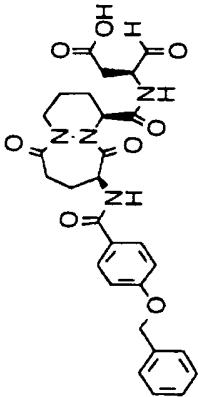
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) +	Syn. Method
484		C25H31N5O8	529.55	7.88 (1) 98%	531	1,2
485		C24H29N5O8	515.53	7.00 (1) 98%	517.6	1,2
486		C29H31N5O8	577.60	10.43 (1) 98%	579.4	1,2

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) <sup>+</sup>	Syn. Method
487		C <sub>26</sub> H <sub>33</sub> N <sub>5</sub> O <sub>8</sub>	543.58	9.30 (1) 98%	545.7	1, 2
488		C <sub>25</sub> H <sub>31</sub> N <sub>5</sub> O <sub>8</sub>	529.55	8.13 (1) 98%	531.1	1, 2
489		C <sub>23</sub> H <sub>28</sub> N <sub>6</sub> O <sub>8</sub>	516.52	5.89 (1) 98%	517.8	1, 4
490		C <sub>23</sub> H <sub>27</sub> N <sub>5</sub> O <sub>9</sub>	517.50	7.27 (1) 98%	(M+Na) 540.8	1, 2



Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) <sup>+</sup>	Syn. Method
491		C28H28N4O9	564.56	12.9 (1) 98%	565.3	1
493		C22H25FN4O8	492.46	8.31 (1) 98%	493.9	1
494		C23H26N4O7	470.49	9.34 (1) 98%	471.2	2

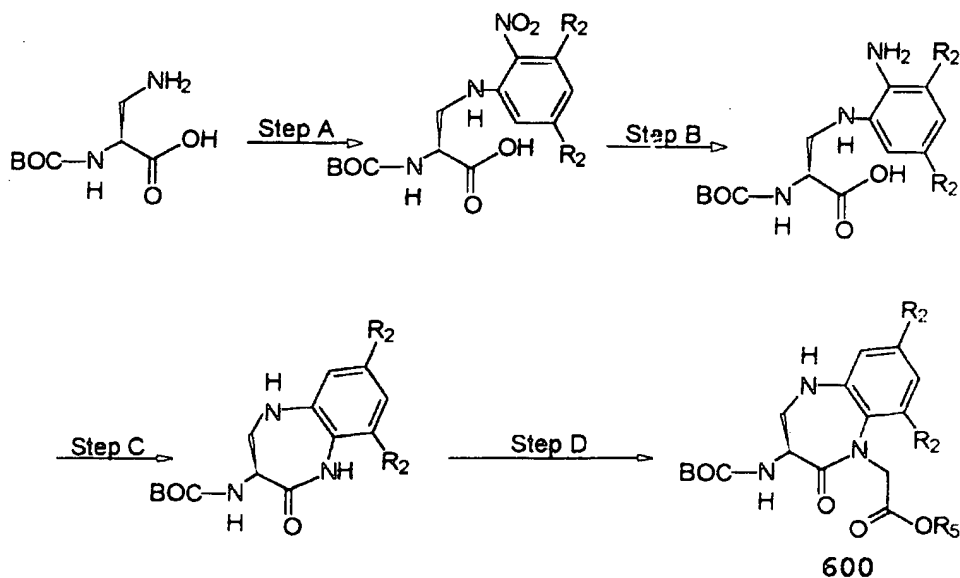
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) <sup>+</sup>	Syn. Method
495		C <sub>22</sub> H <sub>26</sub> N <sub>4</sub> O <sub>7</sub>	458.48	7.24 (1) 98%	459.9	2
496		C <sub>22</sub> H <sub>26</sub> N <sub>4</sub> O <sub>8</sub>	474.47	9.47 (1) 98%	475.7	2
497		C <sub>22</sub> H <sub>25</sub> ClN <sub>4</sub> O <sub>8</sub>	508.92	9.58 (1) 98%	509.5	1
498		C <sub>21</sub> H <sub>23</sub> ClN <sub>4</sub> O <sub>8</sub>	494.89	7.18 (1) 98%	495.1	1

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H) <sup>+</sup>	Syn. Method
499		C28H30N4O8	550.57	13.27 (1) 98%	552	1

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Example 12

Compounds 605a-j, 605m-q, 605s, 605t, and 605v were synthesized as described below.



Compound no.	R <sub>2</sub>	R <sub>5</sub>
600a/103	H	CH <sub>3</sub>
600b	H	CH <sub>2</sub> Ph
600c	CH <sub>3</sub>	CH <sub>2</sub> Ph

(3S)-2-Oxo-3-tert-butoxycarbonylamino-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester (600a/103).

**Step A.** (2S)-2-tert-Butoxycarbonylamino-3-(2-nitrophenyl-amino)-propionic acid. (2S)-2-tert-Butoxycarbonylamino-3-aminopropionic acid (10 g, 49 mmol), 2-fluoronitrobenzene (5.7 ml, 54 mmol), and NaHCO<sub>3</sub> (8.25 g, 98 mmol) was taken into 130 ml of DMF

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and heated at 80 °C for 18 h. The reaction was evaporated *in vacuo* to give a viscous orange residue that was dissolved in 300 ml of H<sub>2</sub>O and extracted with Et<sub>2</sub>O (3 x 150 ml). The aq. solution was acidified to  
5 pH 5 with 10% NaHSO<sub>4</sub> and extracted with EtOAc (3 x 250 ml). The combined extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated to give 12.64 g (83%) of the title compound as an orange amorphous solid: <sup>1</sup>H  
NMR (CD<sub>3</sub>OD) δ 8.15-8.10 (1H, d), 7.54-7.48 (1H, t), 7.13-  
10 7.08 (1H, d), 6.73-6.65 (1H, t), 4.45-4.35 (1H, m), 3.9-3.8 (1H, dd), 3.65-3.55 (1H, dd), 1.45 (9H, s).

**Step B.** (2S)-2-*tert*-Butoxycarbonylamino-3-(2-aminophenyl-amino)-propionic acid. A mixture of (2S)-2-*tert*-Butoxycarbonylamino-3-(2-  
15 nitrophenylamino)propionic acid (12.65 g, 40.5 mmol) and 0.5 g of 10% Pd/C in 100 ml of MeOH under hydrogen at 1 atmosphere was stirred for 4 h. The solution was filtered through Celite 545 and the filtrate evaporated  
in *vacuo* to afford the 11.95 g of the title compound in  
20 quantitative yield as a dark brown solid that was used without purification: <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 6.75-6.70 (3H, m), 6.65-6.58 (1H, m), 4.35-4.3 1H, m), 3.6-3.38 (2H, m), 1.45 (9H, s).

**Step C.** (3S)-2-Oxo-3-*tert*-Butoxycarbonylamino-1,3,4,5-tetrahydro-1H-1,5-benzodiazepine. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride  
25 (8.54 g, 44.5 mmol) was added to a cooled (0 °C) solution of (2S)-2-*tert*-butoxycarbonylamino-3-(2-aminophenylamino)propionic acid (11.95 g, 40.5 mmol) in  
30 100 ml of DMF and stirred for 18 h. The reaction was poured into 700 ml of EtOAc and washed four times with

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100 ml of H<sub>2</sub>O. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated to give a brown solid that was purified by flash chromatography eluting with 3:7 EtOAc/hexane to give 8 g (71%) of the  
5 title compound: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.78 (1H, s), 7.02-6.95 (1H, m), 6.88-6.82 (1H, m), 6.82-6.78 (1H, m), 6.75-6.70 (1H, m), 5.8-5.7 (1H, d), 4.55-4.45 (1H, m), 3.95 (1H, s), 3.9-3.82 (1H, m); 3.48-3.40 (1H, m), 1.45 (9H, s).

10 **Step D. (3S)-2-Oxo-3-tert-butoxycarbonylamino-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester (600a/103).** A 1.0 M solution of lithium bis(trimethylsilyl)amide (3.4 ml, 3.4 mmol) in THF was added dropwise to a -78 °C solution of (3S)-2-oxo-3-  
15 tert-butoxycarbonylamino-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine (0.94 g, 3.38 mmol) in 20 ml of anhydrous THF and stirred for 30 min. Methyl bromoacetate (0.44 ml, 4 mmol) was added dropwise to the reaction mixture then warmed to RT. The reaction  
20 was diluted with 100 ml of EtOAc and washed with 0.3N KHSO<sub>4</sub> (50 ml), H<sub>2</sub>O (2 x 50 ml), and brine. The combined organics were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated to afford a gum that was purified by flash chromatography eluting with 3:7  
25 EtOAc/Hex. to give 0.98 g (83%) of the title compound as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.15-7.07 (2H, m), 6.98-6.94 (1H, m), 6.88-6.84 (1H, d), 5.62-5.55 (1H, d), 4.71-4.65 (1H, d), 4.65-4.6 (1H, m), 4.33-4.27 (1H, d), 3.96-3.90 (1H, m), 3.78 (3H, s), 3.44-3.37 (1H, m),  
30 1.4 (9H, s).

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(3S)-2-Oxo-3-tert-butoxycarbonylamino-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (600b). Prepared by a similar method described for the preparation of 600a/103 (Step D), except benzyl bromoacetate was used instead of methyl bromoacetate to give 600b in quantitative yield.

(3S)-2-Oxo-3-tert-butoxycarbonylamino-2,3,4,5-tetrahydro-7,9-dimethyl-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (600c).

10 Step A. (2S)-2-tert-Butoxycarbonylamino-3-(2-nitro-3,5-dimethylphenylamino)-propionic acid. Prepared by a method similar as described for 600a/103 (Step A), except 2-fluoro-4,6-dimethyl-nitrobenzene was used instead of 2-fluoronitrobenzene to give the desired  
15 compound in 93% yield.

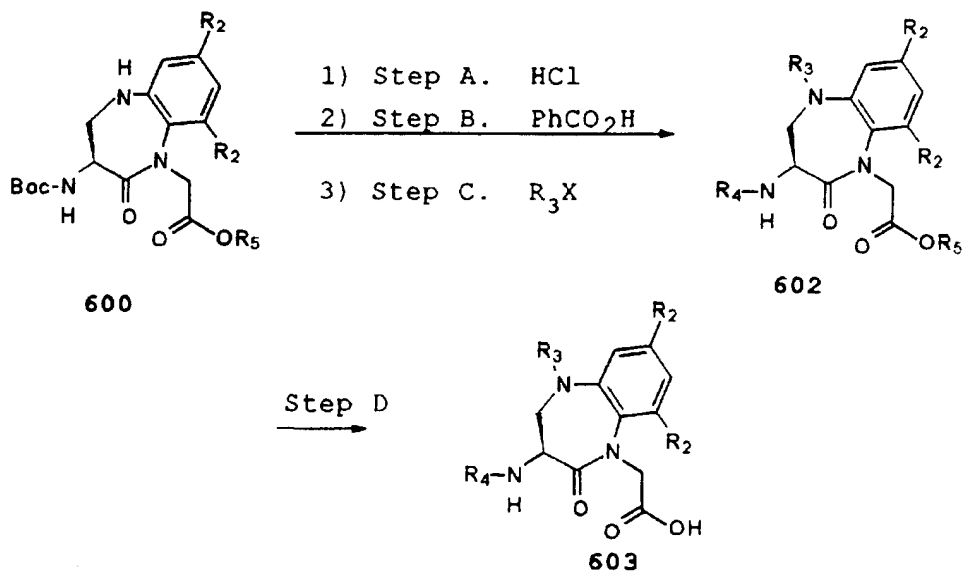
Step B. (2S)-2-tert-Butoxycarbonylamino-3-(2-amino-3,5-dimethylphenyl-amino)-propionic acid. (2S)-2-tert-Butoxycarbonylamino-3-(2-nitro-3,5-dimethylphenyl-amino)propionic acid was converted to the title  
20 compound in quantitative yield as described in the preparation of 600a/103 (Step B).

Step C. 2-Oxo-(3S)-3-tert-butoxycarbonylamino-2,3,4,5-tetrahydro-7,9-dimethyl-1H-1,5-benzodiazepine. A 0 °C solution of (2S)-2-tert-butoxycarbonylamino-3-(2-amino-3,5-dimethylphenyl-amino)-propionic acid (763 mg, 2.36  
25 mmol) and N-methylmorpholine (483 mg, 4.78 mmol) in 60 ml of anhydrous THF was treated dropwise with isobutylchloroformate (352 mg, 2.5 mmol). The reaction was stirred for 2 h at 0 °C, at RT for 1h and poured  
30 over EtOAc. The mixture was washed with aq. 5% NaHSO<sub>4</sub>,

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sat. aq.  $\text{NaHCO}_3$ , and sat. aq.  $\text{NaCl}$ , dried over  $\text{NaSO}_4$ , and concentrated in *vacuo*. Chromatography (flash,  $\text{SiO}_2$ , 10% to 25% to 50 %  $\text{EtOAc}/\text{CH}_2\text{Cl}_2$ ) gave 490 mg (68%) of the desired product.

- 5 **Step D.** (3*S*)-2-Oxo-3-*tert*-butoxycarbonylamino-2,3,4,5-tetrahydro-7,9-dimethyl-1*H*-1,5-benzodiazepine-1-acetic acid benzyl ester (600c). (2*S*)-2-*tert*-Butoxycarbonylamino-3-(2-amino-3,5-dimethylphenyl-amino)-propionic acid was converted to 600c, 75% by a  
10 similar method for the preparation of 600b.



(3*S*)-2-Oxo-3-benzoylamino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid methyl ester (602a).

- 15 **Step A.** Anhydrous  $\text{HCl}$  was bubbled into a solution of (3*S*)-2-oxo-3-*tert*-butoxycarbonylamino-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetic acid methyl ester (600a/103, 4.0 g, 11.4 mmol) in 20 ml of  $\text{CH}_2\text{Cl}_2$  for 20 min then stirred for 1 h at RT. The reaction



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was evaporated to give (3S)-2-oxo-3-amino-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester hydrochloride as a white solid.

**Step B.** The white solid was dissolved in 70 ml of DMF and benzoic acid (1.5 g, 12.3 mmol) was added. The reaction was cooled in a ice/H<sub>2</sub>O bath and treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.4 g, 12.5 mmol), 1-hydroxybenzotriazole (1.7 g, 12.6 mmol) and diisopropylethylamine (3.0g, 23.2 mmol). The reaction was stirred for 18 h at RT under nitrogen atmosphere and poured onto H<sub>2</sub>O. The aq. mixture was extracted with EtOAc (2x). The combined organic layers were washed with aq. 0.5 N NaHSO<sub>4</sub>, H<sub>2</sub>O, sat. aq. NaHCO<sub>3</sub>, H<sub>2</sub>O and sat. aq. NaCl, dried over MgSO<sub>4</sub> and concentrated *in vacuo*. Chromatography (flash, SiO<sub>2</sub>, 10% to 30% EtOAc/CH<sub>2</sub>Cl<sub>2</sub>) gave 3.4 g (85%) of (3S)-2-oxo-3-(benzoylamino)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester as a white solid.

**Step C. Method A.** (3S)-2-Oxo-3-benzoylamino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester (602a). A solution of (3S)-2-oxo-3-(benzoylamino)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester (200 mg, 0.57 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 ml) was treated with triethylamine (119 mg, 1.13 mmol) and 3-phenylpropionyl chloride (114 mg, 0.68 mmol). The reaction was stirred at RT for 30 min and diluted with CH<sub>2</sub>Cl<sub>2</sub>. The solution was washed with aq. 10% HCl, sat. aq. NaHCO<sub>3</sub> and sat. aq. NaCl, dried over Na<sub>2</sub>SO<sub>4</sub> and

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concentrated *in vacuo* to give 240 mg (87%) of **602a** as a white foam.

**Step C. Method B. (3S)-2-Oxo-3-benzoylamino-5-acetoacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (602g).** A 0 °C solution of (3S)-2-oxo-3-(benzoylamino)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (**600b**) (465 mg, 1.10 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) was treated with acetoacetic acid in 1 ml of CH<sub>2</sub>Cl<sub>2</sub> followed by slow addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (431 mg, 2.2 mmol) in 2 ml of CH<sub>2</sub>Cl<sub>2</sub> under N<sub>2</sub> atmosphere. After 15 min the reaction was poured onto EtOAc, washed with aq. 5 % NaHSO<sub>4</sub>, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. Chromatography (flash, SiO<sub>2</sub>, 0% to 10% to 25% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) gave 580 mg of (3S)-2-oxo-3-(benzoylamino)-5-acetoacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester as a white solid.

**Step C. Method C. (3S)-2-Oxo-3-benzoylamino-5-methoxycarbonyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (602j).** A vigorously-stirred, 0 °C solution of (3S)-2-oxo-3-(benzoylamino)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (**600b**) (461 mg, 1.07 mmol) in THF (5 ml) and sat. aq. NaHCO<sub>3</sub> (2.5 ml) was treated with a THF solution (0.35 ml) of methyl chloroformate (151 mg, 1.6 mmol) and the reaction was stirred for 45 min at RT. The reaction was poured onto CH<sub>2</sub>Cl<sub>2</sub> and washed with H<sub>2</sub>O, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. Chromatography

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(flash, SiO<sub>2</sub>, 0% to 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) gave 525 mg of 602j as a white solid.

**Step C. Method D. (3S)-2-Oxo-3-benzoylamino-5-benzylaminocarbonyl-2,3,4,5-tetrahydro-1H-1,5-**

5 **benzodiazepine-1-acetic acid methyl ester (602p).** A solution of 600a/103 (400 mg, 1.1mmol) and benzylisocyanate (166 mg, 1.2mmol) in 10 ml of CH<sub>2</sub>Cl<sub>2</sub> and 10 ml of DMF and heated at 80 °C for 3 days. The reaction was cooled to RT poured onto H<sub>2</sub>O and extracted  
10 with EtOAc (2x). The combined organic layers were washed with H<sub>2</sub>O (4x) and sat. aq. NaCl, dried over MgSO<sub>4</sub> and concentrated *in vacuo*. Chromatography (flash, SiO<sub>2</sub>, 50% to 80% EtOAc/hexane) gave 440 mg (80%) of 602p as a white solid.

15 **Step C. Method E. (3S) 2-Oxo-3-benzylamino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester (602v).** A solution of (3S) 2-oxo-3-amino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid  
20 methyl ester hydrochloride (560 mg, 1.34 mmol), benzaldehyde (146 mg, 1.34 mmol) and sodium acetate (220 mg, 2.68 mmol) in methanol (20 ml) was treated with 4Å sieves (2 g) and NaCNBH<sub>3</sub> (168 mg, 2.68 mmol). The reaction was stirred for 2.5 h, acidified with 10%  
25 aq. HCl to pH 2 and washed with Et<sub>2</sub>O (2x75 ml). The organic layers were concentrated *in vacuo* to give an oil. Chromatography (flash, SiO<sub>2</sub>, 0 to 35% EtOAc/CH<sub>2</sub>Cl<sub>2</sub>) gave 250 mg (40%) of 602v as a clear oil.

**Step D. Method A. (3S)-2-Oxo-3-benzoylamino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-**

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benzodiazepine-1-acetic acid (603a). (3S)-2-Oxo-3-benzoylamino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester (602a; 1.25 g, 2.57 mmol) was dissolved in 11 ml of THF, MeOH and H<sub>2</sub>O (5:5:1) and treated with LiOH·H<sub>2</sub>O (42 mg, 0.62 mmol) stirred at RT for 64 h. The reaction was concentrated *in vacuo*, diluted with H<sub>2</sub>O and acidified with aq. 1N HCl to give 230 mg of 603a as a white solid.

10 **Step D. Method B.** (3S) 2-Oxo-3-benzoylamino-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid (603d). A mixture of (3S)-2-oxo-3-(benzoylamino)-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (602d; 510 mg, 1.08 mmol) and 5% Pd/C (250 mg) in MeOH (10 ml) stirred under H<sub>2</sub> (1 atm) for 0.5h. The reaction was filtered and concentrated *in vacuo* 410 mg of 603d as a white solid.

The compounds of Table 8 were prepared as described in Table 9, using the methods of Example 12.

20 **Table 8**

Compound no.	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>
602b	H	PhCH <sub>2</sub> C(O)	PhC(O)	CH <sub>2</sub> Ph
602c	H	PhC(O)	PhC(O)	CH <sub>2</sub> Ph
25 602d	H	CH <sub>3</sub> C(O)	PhC(O)	CH <sub>2</sub> Ph
602e	H	CH <sub>3</sub> OCH <sub>2</sub> C(O)	PhC(O)	CH <sub>2</sub> Ph
602f	H	(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub> C(O)	PhC(O)	CH <sub>2</sub> Ph
602g	H	CH <sub>3</sub> C(O)CH <sub>2</sub> C(O)	PhC(O)	CH <sub>2</sub> Ph

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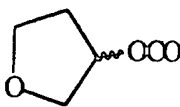
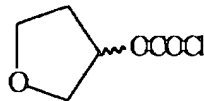
Compound no.	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>
602h	H	CH <sub>3</sub> OC(O)C(O)	PhC(O)	CH <sub>2</sub> Ph
602i	H	CH <sub>3</sub> C(O)C(O)	PhC(O)	CH <sub>2</sub> Ph
602j	H	CH <sub>3</sub> OC(O)	PhC(O)	CH <sub>2</sub> Ph
602k	H	CH <sub>3</sub> C(O)	Boc	CH <sub>2</sub> Ph
5 602l	CH <sub>3</sub>	CH <sub>3</sub> C(O)	Boc	CH <sub>2</sub> Ph
602m	H	CH <sub>3</sub> S(O <sub>2</sub> )	PhC(O)	CH <sub>3</sub>
602p	H	PhCH <sub>2</sub> NHC(O)	PhC(O)	CH <sub>3</sub>
602q	H		PhC(O)	CH <sub>2</sub> Ph
602r	H	PhCH <sub>2</sub> CH <sub>2</sub> C(O)	PhCH <sub>2</sub> CH <sub>2</sub> C(O)	CH <sub>2</sub> Ph
10 602s	H	4-pyridylCH <sub>2</sub> C(O)	PhC(O)	CH <sub>2</sub> Ph

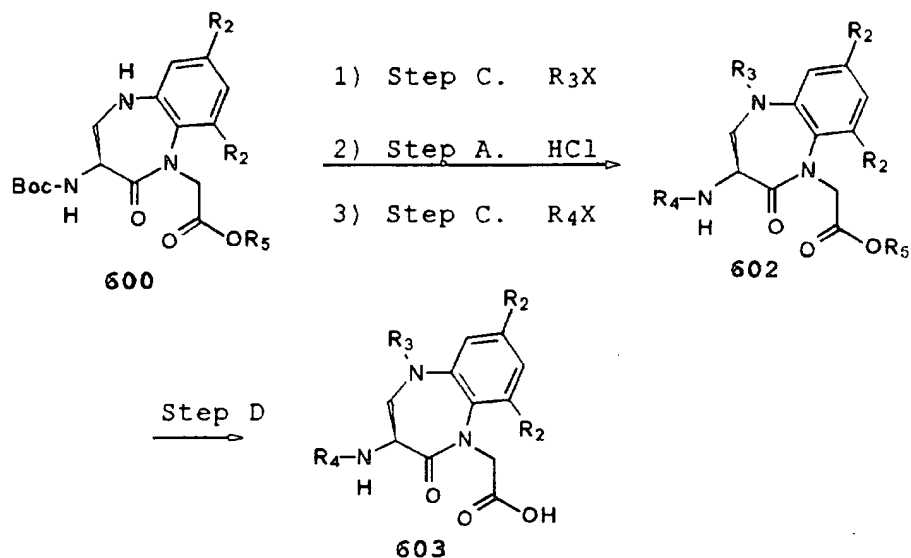
Table 9

No.	Starting material	R <sub>3</sub> X	Step C method/ (% yield)	Step D method/ (% yield)
603b	600b	PhCH <sub>2</sub> C(O)Cl	A (98)	B (89)
603c	600b	PhC(O)Cl	A (quant.)	B (quant.)
15 603d	600b	CH <sub>3</sub> C(O)Cl	A (quant.)	B (quant.)
603e	600b	CH <sub>3</sub> OCH <sub>2</sub> C(O)Cl	A (59)	B (quant.)
603f	600b	(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub> C(O)Cl	A (88)	B (95)
603g	600b	CH <sub>3</sub> C(O)CH <sub>2</sub> CO <sub>2</sub> H	B (quant.)	B (quant.)
603h	600b	CH <sub>3</sub> OC(O)C(O)Cl	A (96)	B (quant.)
20 603i	600b	CH <sub>3</sub> C(O)CO <sub>2</sub> H	B (87)	B (94)
603j	600b	CH <sub>3</sub> OC(O)Cl	C (quant.)	B (quant.)

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No.	Starting material	R <sub>3</sub> X	Step C method/ (% yield)	Step D method/ (% yield)
603k	600b	CH <sub>3</sub> C(O)Cl	A, Step C only (quant.)	not run
603l	600c	CH <sub>3</sub> C(O)Cl	A, Step C only (quant.)	not run
603m	600a/103	CH <sub>3</sub> SO <sub>3</sub> Cl, NEt <sub>3</sub> instead of pyridine and THF instead of CH <sub>2</sub> Cl <sub>2</sub>	A (76)	A (92)
603p	600a/103	PhCH <sub>2</sub> C=N=O	D (80)	A (86)
603q	600b		C (83)	B (71)
603r	600a/103	PhCH <sub>2</sub> CH <sub>2</sub> C(O)Cl	A	
603s	600b	4-pyridylCH <sub>2</sub> CO <sub>2</sub> H	B (90)	B (98)

5



The compounds of Table 10 were prepared as described in Table 11 using the methods of Example 12.

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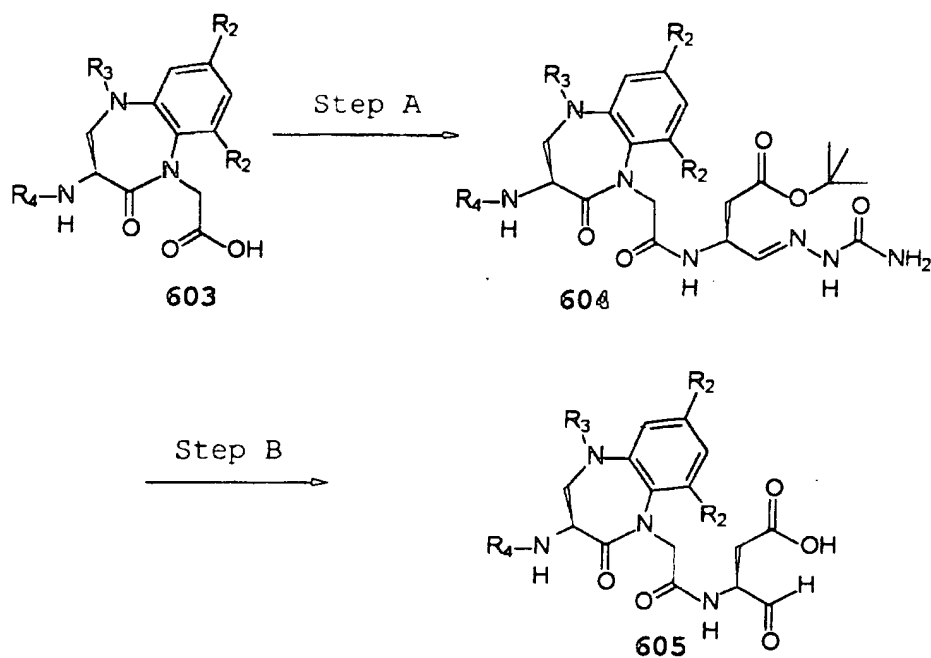
Table 10

Compound no.	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>
602n	H	CH <sub>3</sub> C(O)	Naphthylene-2-C(O)	CH <sub>2</sub> Ph
602o	CH <sub>3</sub>	CH <sub>3</sub> C(O)	PhC(O)	CH <sub>2</sub> Ph
602t	H	3-CH <sub>3</sub> PhCH <sub>2</sub> C(O)	PhC(O)	CH <sub>2</sub> Ph
602u	H	CH <sub>3</sub> C(O)	Fmoc	CH <sub>2</sub> Ph
602v	H	PhCH <sub>2</sub> CH <sub>2</sub> CO	PhCH <sub>2</sub>	CH <sub>3</sub>

Table 11

No.	Starting material	1) Step C. R <sub>3</sub> X method (% yield)	3) Step C R <sub>4</sub> X method (% yield)	Step D method (% yield)
603n	602k	CH <sub>3</sub> C(O)Cl A (quant.)	naphthylen e- 2-C(O)Cl A (70)	B (quant.)
603o	602l	CH <sub>3</sub> C(O)Cl A (quant.)	PhC(O)Cl A (73)	B (quant.)
603t	602k	3- CH <sub>3</sub> PhCH <sub>2</sub> C(O)Cl A (quant.)	PhC(O)Cl A (93)	B (95)
603u	602k	CH <sub>3</sub> C(O)Cl A (quant.)	Fmoc-Cl C (82)	C (98)
603v	600a/103	PhCH <sub>2</sub> CH <sub>2</sub> C(O)Cl A	PhCHO E (40)	A (95)

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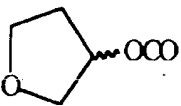
The compounds of Table 12 were prepared by the methods described below.

Table 12

compound no.	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>
605a	H	PhCH <sub>2</sub> CH <sub>2</sub> C(O)	PhC(O)
605b	H	PhCH <sub>2</sub> C(O)	PhC(O)
605c	H	PhC(O)	PhC(O)
605d	H	CH <sub>3</sub> C(O)	PhC(O)
605e	H	CH <sub>3</sub> OCH <sub>2</sub> C(O)	PhC(O)
605f	H	(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub> C(O)	PhC(O)
605g	H	CH <sub>3</sub> C(O)CH <sub>2</sub> C(O)	PhC(O)
605h	H	CH <sub>3</sub> OC(O)C(O)	PhC(O)
605i	H	CH <sub>3</sub> C(O)C(O)	PhC(O)
605j	H	CH <sub>3</sub> OC(O)	PhC(O)



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compound no.	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>
605m	H	CH <sub>3</sub> SO <sub>3</sub>	PhC(O)
605n	H	CH <sub>3</sub> C(O)	Naphthyl-2-C(O)
605o	CH <sub>3</sub>	CH <sub>3</sub> C(O)	PhC(O)
605p	H	PhCH <sub>2</sub> NHC(O)	PhC(O)
605q	H		PhC(O)
605s	H	4-pyridylCH <sub>2</sub> C(O)	PhC(O)
605t	H	3-CH <sub>3</sub> PhCH <sub>2</sub> C(O)	PhC(O)
605v	H	PhCH <sub>2</sub> CH <sub>2</sub> C(O)	PhCH <sub>2</sub>

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605a).

**Step A.** (3S)-3-(1-Fluorenylmethyloxycarbonylamino)-4-oxobutyric acid tert-butyl ester semicarbazone (210 mg, 0.45 mol, Prepared in a similar manner to the benzyloxycarbonyl analog in Graybill et al., Int. J. Protein Res., 44, pp. 173-82 (1994).) was dissolved in 10 ml of DMF and 2 ml of diethylamine and stirred for 2 h. The reaction was concentrated *in vacuo* to give (3S)-3-amino-4-oxobutyric acid tert-butyl ester semicarbazone. The 0 °C solution of the above residue and **603a** (200 mg, 0.42mmol) in 5 ml of DMF and 5 ml of CH<sub>2</sub>Cl<sub>2</sub> was treated with 1-hydroxybenzotriazole (57 mg, 0.42mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (98 mg, 0.51 mmol). The reaction was stirred at RT for 18 h, poured onto

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EtOAc (75 ml) and washed with aq. 0.3 N KHSO<sub>4</sub>, sat. aq. NaHCO<sub>3</sub> and sat. aq. NaCl, dried over NaSO<sub>4</sub> and concentrated *in vacuo*. Chromatography (flash, SiO<sub>2</sub>, 0% to 4% MeOH/0.1% NH<sub>4</sub>OH/CH<sub>2</sub>Cl<sub>2</sub>) to give 240 mg (83%) of  
5 **604a**.

**Step B.** **604a** was stirred with 10 ml of 33% TFA/H<sub>2</sub>O for 4 h and concentrated *in vacuo*. The residue was dissolved in 7 ml of MeOH/acetic acid/37% aq. formaldehyde (5:1:1) and stirred for 18 h.  
10 Chromatography (Reverse Phase C18, 4.4mm ID x 25 cm, 15% to 70% CH<sub>3</sub>CN/0.1% TFA/H<sub>2</sub>O) gave 32 mg (16%) of **605a** as a white solid: <sup>1</sup>H NMR (CD<sub>3</sub>OD, existing as diastereomers of the hemiacetal) δ 7.85-7.78 (2H, d), 7.5-7.32 (6H, m), 7.32-7.28 (1H, m), 7.18-6.98 (5H, m),  
15 4.92-4.85 (2H, m), 4.5-4.32 (2H, m), 4.31-4.20 (2H, m), 3.7-3.6 (1H, m), 2.90-2.75 (2H, m), 2.65-2.5 (1H, m), 2.48-2.25 (3H, m).

The following compounds were prepared by a similar method:

20 **(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-phenylacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605b)**. 148 mg (33%) as a white solid: <sup>1</sup>H NMR(CD<sub>3</sub>OD) δ 7.9-6.9 (m, 16H), 4.9 (s, 2H), 4.5 (m, 1H), 4.4 (m, 2H), 3.75 (s, 1H), 3.6  
25 (dd, 1H), 3.45 (dd, 1H), 2.7 (m, 1H), 2.5 (m, 1H).

**(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-benzoyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605c)**. 319 mg (56%) as a white solid: <sup>1</sup>H NMR(CD<sub>3</sub>OD) δ 7.9-6.9 (m, 16H), 5.1 (m, 1H), 4.9 (dd,

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1H), 4.7 (m, 1H), 4.6 (dd, 1H), 4.4 (m, 2H), 4.05 (m, 1H), 2.7 (m, 1H), 2.5 (m, 1H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyr  
5 ic acid (605d). 190 mg (38%) as a white solid: <sup>1</sup>H NMR(CD<sub>3</sub>OD) δ 1.9(d, H), 2.4(m, 1H), 2.65(m, 1H), 3.7(m, 1H), 4.25(m, 1H), 4.45(m, 2H), 4.8-5.05(m, 3H), 7.3-7.7(m, 7H), 7.9(d, 2H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-methoxyacetyl-  
10 2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyr  
ic acid (605e). 250 mg (78%) <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 1.87 (bs), 1.95 (s, 2H), 2.1 (bs), 2.4 (m, 2H), 2.65 (m, 2H), 3.59 (bs), 3.75 (bs), 3.87 (bs), 4.19 (m), 4.37 (m), 4.50-4.78 (bm), 4.92 (m), 5.27  
15 (bs), 7.41-7.58 (m, 7H), and 7.87 ppm (d, 2H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-(3-methylbutyryl)-  
2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyr  
ic acid (605f). 210.5 mg (46%) as a white solid: <sup>1</sup>H NMR(CD<sub>3</sub>OD) δ 7.9-7.4 (m, 9H), 5.1  
20 (m, 1H), 4.9 (m, 1H), 4.6 (dd, 1H), 4.4 (m, 2H), 4.1 (d, 1H), 3.8 (m, 1H), 3.5 (q, 1H), 2.7 (m, 1H), 2.5 (m, 1H), 2.0 (m, 3H), 1.2 (t, 1H), 0.9 (d, 3H), 0.8 (d, 3H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-acetoacetyl-  
25 2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyr  
ic acid (605g). 81 mg (19%) as a white solid: <sup>1</sup>H NMR(CD<sub>3</sub>OD) δ 7.9-7.3 (m, 11H), 4.9-4.8 (m, 2H), 4.6-4.4 (m, 3H), 4.3 (m, 1H), 3.75 (q,

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1H), 3.55 (d, 1H), 2.7 (m, 1H), 2.5 (m, 1H), 2.05 (s, 3H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-methyloxalyl-  
2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-

5 acetylamino]4-oxo-butyric acid (605h). 227 mg (54%) of  
a white solid: <sup>1</sup>H NMR(CD<sub>3</sub>OD) δ 2.5(m, 1H), 2.7(m, 1H),  
3.55(s, 3H), 3.8-4.0(m, 2H), 4.4(m, 1H), 4.6-4.8(m,  
2H), 4.95(d, 1H), 5.1(m, 1H), 7.3-7.7(m, 7H), 7.9(d,  
2H), 8.6(d, 1H).

10 (3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-acetylcarbonyl-  
2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-

acetylamino]4-oxo-butyric acid (605i). 150 mg (37%) as  
a white solid: <sup>1</sup>H NMR(CD<sub>3</sub>OD) δ 7.9-7.3 (m, 12H), 5.1  
(m, 1H), 4.65 (t, 1H), 4.55 (dd, 1H), 4.35 (m, 1H), 4.1  
15 (d, 1H), 3.9 (q, 1H), 3.45 (q, 1H), 2.7 (m, 1H), 2.5  
(m, 1H), 2.25 (s, 3H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-methoxycarbonyl-  
2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-

acetylamino]4-oxo-butyric acid (605j). 234 mg (44%) as  
20 a white solid: <sup>1</sup>H NMR(CD<sub>3</sub>OD) δ 7.9-7.4 (m, 12H), 5.0  
(m, 1H), 4.8-4.5 (m, 3H), 4.4 (m, 1H), 4.3 (t, 1H),  
3.9-3.75 (m, 2H), 3.6 (s, 3H), 2.7 (m, 1H), 2.5 (m,  
1H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-methanesulfonyl-

25 2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-

acetylamino]4-oxo-butyric acid (605m). 64.5 mg (34%)  
as a white solid: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, existing as  
diastereomers of the hemiacetal & open form of the  
aldehyde) δ 9.48 (0.2H, s), 8.85-8.72 (1H, m), 8.65-

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8.60 (0.8 H, d), 8.30-8.26 (0.2 H, d), 7.95-7.88 (2H, d), 7.6-7.45 (6H, m), 7.44-7.38 (1H, m), 5.78-5.75 (0.2H, d), 5.48 (0.6H, s), 4.85-4.70 (2H, m), 4.62-4.54 (1H, d), 4.50-4.40 (2H, m), 4.25-4.14 (1H, m), 3.9-3.85 (1H, m), 3.16 (3H, s), 3.05-2.3 (2, m).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-(naphthlene-2-carbonyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetyl amino]4-oxo-butyric acid (605n). 103 mg (17%) as a white solid: <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 1.9(s, 3H), 2.5(m, 1H), 2.65(m, 1H), 3.75(m, 1H), 4.3(m, 1H), 4.5-4.7(m, 3H), 4.85-5.1(m, 2H), 7.3-7.65(m, 6H), 7.85-8.05(m, 4H), 8.45(s, 1H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-acetyl-2,3,4,5-tetrahydro-7,9-dimethyl-1H-1,5-benzodiazepin-1-acetyl amino]4-oxo-butyric acid (605o). 42 mg (12%) as a white solid: <sup>1</sup>H NMR (CD<sub>3</sub>OD, existing as diastereomers of the hemiacetal) δ 7.85-7.74 (2H, m), 7.5-7.44 (1H, m), 7.43-7.35 (4H, m), 5.6-5.05 (2H, m), 4.82-4.42 (2H, m), 4.40-3.95 (2H, m), 3.6-3.5 (1H, m), 2.7-2.38 (2H, m), 2.32 (3H, s), 2.27 (3H, s), 1.92 (3H, s).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-benzylaminocarbonyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetyl amino]4-oxo-butyric acid (605p). 165 mg (37%) as a white solid: <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 2.45(m, 1H), 2.7(m, 1H), 3.8(m, 1H), 4.15-4.5(m, 4H), 4.5-4.75(m, 2H), 4.8-5.0(m, 2H), 7.1-7.7(m, 12H), 7.9(d, 2H).

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(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-[(3R,S) 3-tetrahydrofuranylmethoxycarbonyl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605q). 210 mg (66%) <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 1.95 (s, 2H),

5 2.4 (m, 2H), 2.65 (m, 2H), 3.29 (s, 3H), 3.78 (m), 3.87 (bs), 4.0 (d, 1H), 4.32 (m), 4.50-4.15 (m), 4.95 (m), 5.27 (bs), 7.45-7.65 (m, 7H), and 7.89 ppm (d, 2H).

(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-(4-pyridylacetyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-

10 acetylamino]4-oxo-butyric acid (605s). 128 mg (19%) as a white solid: <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 8.5-7.4 (m, 13H), 5.0 (m, 1H), 4.7 (m, 1H), 4.5 (m, 2H), 4.45-4.4 (m, 3H), 3.8-3.7 (m, 2H), 2.7 (m, 1H), 2.5 (m, 1H).

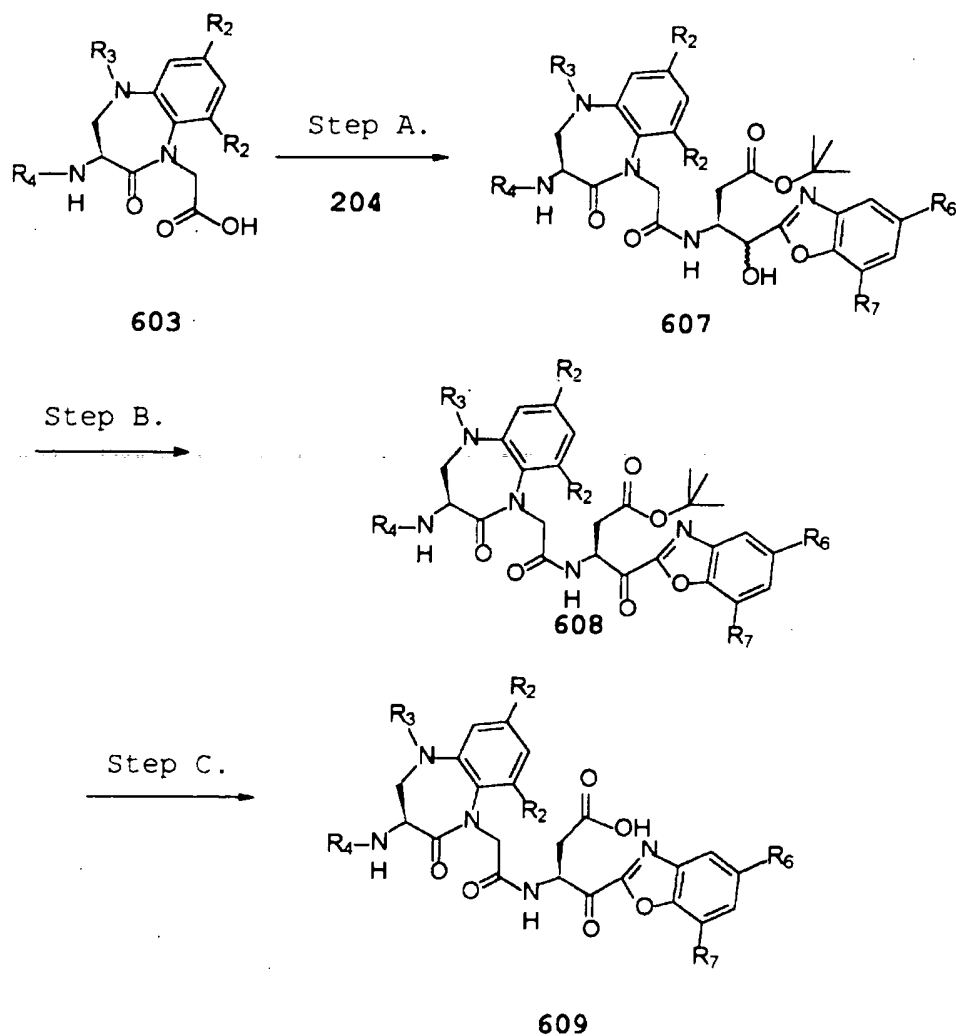
(3S)-3-[(3S)-2-Oxo-3-benzoylamino-5-(3-

15 methylphenylacetyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid (605t). 132 mg (24%) as a white solid: <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.8-6.7 (m, 13H), 4.9 (t, 1H), 4.75 (dd, 1H), 4.2 (dd, 1H), 4.1 (m, 2H), 3.8 (dd, 1H), 3.6 (q, 1H), 3.45 (dd, 1H), 3.3 (dd, 1H), 2.6 (m, 1H), 2.3 (m, 1H), 2.15 (s, 3H).

(3S) 3-[(3S) 2-Oxo-3-benzylamino-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]4-oxo-butyric acid trifluoroacetic acid salt (605v). 88 mg (28%) as a white solid: <sup>1</sup>H NMR

25 (CD<sub>3</sub>OD) δ 7.63-7.51 (2H, m), 7.5-7.35 (7H, m), 7.25-7.10 (3H, m), 7.1-7.02 (2H, m), 5.04-4.96 (1H, m), 4.75-4.57 (2H, m), 4.38-4.30 (2H, m), 4.24-4.12 (2H, m), 4.10-4.02 (1H, d), 4.88-4.80 (1H, m), 2.90-2.80 (2H, m), 2.78-2.63 (1H, m), 2.55-2.35 (2H, m), 2.34-2.22 (1H, m).

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The compounds of Table 13 are described below.

**Table 13**

#	$R_2$	$R_3$	$R_4$	$R_6$	$R_7$
609a	H	$\text{PhCH}_2\text{CH}_2\text{C(O)}$	$\text{PhCH}_2\text{CH}_2\text{C(O)}$	Cl	Cl
609b	H	$\text{CH}_3\text{C(O)}$	$\text{PhC(O)}$	Cl	Cl

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(3S)-3-[(3S)-2-Oxo-3-(3-phenylpropionylamino)-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]-4-(5,7-dichlorobenzoxazol-2-yl)-4-oxo-butyric acid (609a).

- 5 **Step A.** A solution of 204 (223 mg, 0.5 mmol) and 603r (300mg; 0.36 mmol) in 4 ml of DMF and 4 ml of CH<sub>2</sub>Cl<sub>2</sub> was treated with (Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub> (10 mg), 1-hydroxybenzotriazole (135 mg, 1.0 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride  
10 (115 mg, 0.6 mmol). Tri-n-butyl tin hydride (219 mg, 0.75 mmol) was added dropwise to the reaction and stirred for 18 h. The reaction was poured onto EtOAc and washed with aq. 10% NaHSO<sub>4</sub>, sat. aq. NaHCO<sub>3</sub> and sat. aq. NaCl, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in  
15 vacuo. Chromatography (flash, SiO<sub>2</sub>, 0% to 50% EtOAc/hexane) gave 360 mg (86%) of 607a as a foam.

- Step B.** A solution of 607a (360 mg) in 5 ml of CH<sub>2</sub>Cl<sub>2</sub> was added dropwise to a suspension of 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodioxol-3(1H)-one (362 mg, 0.85  
20 mmol) in 20 ml of CH<sub>2</sub>Cl<sub>2</sub>. The reaction was stirred for 4.5 h, diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with a 1:1 mixture of sat. aq. NaHCO<sub>3</sub>/sat. aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, sat. aq. NaHCO<sub>3</sub> (2x) and sat. aq. NaCl, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo. Chromatography (flash, SiO<sub>2</sub>,  
25 20% EtOAc/CH<sub>2</sub>Cl<sub>2</sub>) gave 340 mg (95%) of the ketone 608a.

- Step C.** 608a (300 mg, 0.36 mmol) was dissolved in 25 ml of 25% TFA/CH<sub>2</sub>Cl<sub>2</sub> and stirred at RT for 5 h and concentrated in vacuo. Chromatography (flash, SiO<sub>2</sub>, 0 to 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) gave 118 mg (42%) of 609a as a white  
30 solid: <sup>1</sup>H NMR (CD<sub>3</sub>OD) δ 7.62-6.65 (16H, m), 4.85-4.7